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VOLUME 1 MARCH, 1928 NUMBER 9

ANNALS OF INTERNAL MEDICINE

PUBLISHED BY

The American College of Physicians

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Issued Monthly

ANN ARBOR, MICHIGAN

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PATHOLOGY DEPARTMENT.

ANNALS OF INTERNAL MEDICINE

OFFICIAL PERIODICAL OF THE AMERICAN COLLEGE OF PHYSICIANS

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DEPARTMENT OF REVIEWS

The Journal will make an especial feature of the review of monographs and books bearing upon th field of Internal Medicine. Authors and publishers wishing to subject such material for the purpos of review should send it to the editor. While obviously impossible to make extended reviews of al material, an acknowledgment of all matter sent will be made in the department of reviews.

Editor

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Price per volume, net, postpaid, $7.00, United States, Canada, Mexico, Cuba, $7.50 other countries

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Gastro-Duodenal Hemorrhage*

By Frank Smithies, M.D., Sc.D., *Chicago, Illinois*

BLEEDING from the stomach may be acute and copious or chronic and of small amount. Both forms of hemorrhage may be continuous or intermittent. A combination of the grades is possible. Sudden, copious gastric hemorrhage commonly leads to blood vomiting (*hematemesis*) and to blood-stained stools (*melena*). However, even extensive gastrorrhagia may be unaccompanied by hematemesis, but may be associated with melena alone. Chronic seepage of small quantities of blood is, of itself, rarely productive of hematemesis. While this form of gastrorrhagia may give rise to obvious melena, quite commonly the presence of blood pigment in the stools can only be demonstrated by chemical, microscopic or spectroscopic tests (so-called "altered" or "occult" *hemorrhage*.

Case-Briefs Illustrating Clinical and Pathological States Associated with Gastrorrhagia.

Case I.—A male, aged 49, had been annoyed for two years with a gradually increasing painless dysphagia. Recently, solids lay "like a lump of lead at the pit of the stomach" and fluids were swallowed and retained only by vigorous and continued gulping manoeuvres. Suddenly following the ingestion of peanuts at a ballgame, large quantities of dark red, unclotted blood were vomited; bleeding persisted, exsanguination seemed imminent and the man was brought by police ambulance to the hospital.

Physical examination was negative apart from signs attendant upon acute hemorrhage, with the exception of a moderately large, hard, rough-surfaced liver. A working diagnosis of non-malignant obstruction at the cardia, in association with cirrhosis of the liver was made. Later, lues was proved, hepatitis established and fibrous stenosis of the lower esophagus demonstrated.

The hemorrhage was attributed to rupture of sinus-like veins near the cardia. Specific therapy was pushed. The patient is alive and rugged after eleven and one-half years. A moderate degree of dysphagia persists.

Case II.—A male, aged 64, who had been subjected to long duration radium treatments for suspected cancer of the prostate gland, and following which was "greatly prostrated and hospitalized for this" for sixteen weeks, on arising one morning, experienced sudden dizziness, "pounding of the heart" and, without any pain, vomited a large amount of fluid and clotted blood. Under rest and starvation bleeding ceased in three days and never recurred. A month afterwards, painless hematuria appeared and persisted for a week. The catheterized urine contained, in addition to blood cells, practically a pure culture of non-hemolytic

*A Clinical Lecture Delivered at The Inter-State Post-Graduate Medical Association of North America at Kansas City, October 18, 1927.

streptococci in short chains. Six weeks after the hematuria the man became febrile, the attack lasting several days, he had pain in the left axillary zone and coughed up bloody mucoid material for a week.

Physically, the axillary region exhibited an irregular area of airless lung tissue, fine moist râles, but no well-defined consolidation. The bloody sputum contained non-hemolytic streptococci in clumps and short chains.

When examined by the writer a heart in early decompensation was present, the myocardial weakness being aggravated by an advanced mitral regurgitation. Blood culture made on the third day of a febrile stage of the patient's illness showed, after four days, non-hemolytic streptococci growing in short chains.

Explanation of the gastric hemorrhage appeared to lie in this man's being affected with a subacute bacterial endocarditis from which septic emboli were carried away in the blood stream, producing embolism successively in the gastric wall, the kidney and lung (infarction).

Case III.—A female, aged 24, was admitted during a most alarming gastric hemorrhage. She was in good flesh, very restless, apprehensive and loquacious. She was menstruating profusely at time of entry. The gastrorrhagia had appeared following severe epigastric pain.

The abdomen exhibited 4 surgical scars: two in the upper right quadrant, one in the right lower quadrant and one above the pubis. There was a history of five abdominal sections: an appendectomy, a uterine "suspension," an operation for "ovarian cysts," a plastic operation upon the pylorus for suspected peptic ulcer (no ulcer demonstrated) and within the past year, a gastroenterostomy for suspected "hidden ulcer" (none demonstrable).

The operative procedures were carried out to relieve dysmenorrhea and, during the past four years, a digestive disturbance. In association with the dyspepsia, over a period of three years, there had been nine severe gastric hemorrhages. *These hemorrhages had always occurred during or before a menstrual cycle.* Peptic ulcer had been diagnosed—several Leube-Sippy treatments had been instituted with no benefit and finally surgical exploration had been performed. Careful search failed to reveal peptic ulcer, but operative procedures were performed "on suspicion." Three hemorrhages, excluding the one for which the patient came under our observation, had occurred since the pyloric plastic surgery and the gastroenterostomy.

Explanation of the gastrorrhagia: a "vicarious" bleeding, supplementing menstruation.

The patient was advised regarding the nature of her ailment; matrimony and child bearing were suggested. Her subsequent history was another severe hemorrhage, for which one-third of the stomach was removed "on suspicion." While convalescing from the pylorectomy, menstruation occurred, and with it, a most copious hemorrhage. The patient finally married, quickly became pregnant and since pregnancy, has experienced neither dysmenorrhea of gastrorrhagia. She has borne four children in seven years.

Case IV.—A male, aged 36, experienced vague gastric discomfort, became dizzy and vomited a large volume of fluid and clotted blood. A diagnosis of peptic ulcer was made and a Leube-Sippy regime instituted. Soon after leaving the hospital "cured," another copious hematemesis occurred and the patient came under our care.

Physically, apart from signs of severe blood loss, there were demonstrated a firm, tender spleen extending a hand's breadth below the left thoracic margin, an enlarged, smooth-surfaced liver, palpable for three fingers-breadth below the ribs and a tender area over the anatomic region of the gall-bladder. The stool contained entameba histolytica. The anemia was of "secondary" type; there was blood-derived pigment in the urine. By x-ray and otherwise, the alimentary tract was entirely negative.

The patient gave history of serving as a soldier in the Spanish-American War. In Cuba he experienced malaria and "dysen-

tery." He had been anemic since these affections.

Explanation of Gastrorrhagia: Splenic anemia and Banti's syndrome (chronic malaria? systemic amebiasis?).

The subsequent history included splenectomy following an exsanguinating hemorrhage; blood transfusions; cholecystectomy and later operation for common duct stones; treatment of intestinal amebiasis. The patient lived and was active as a physician for more than twenty years, but recently died from uncontrollable gastric hemorrhage.

Case V.—A female, aged 23, appeared for the relief of several attacks of vomiting of material which "looked like red ink." The emesis was painless but was preceded by nausea, full feeling in head and dizziness. The patient is a chemist and for several months has been conducting research upon very volatile oil distillates. She had no vomiting or other digestive disturbance prior to engaging in her present research.

Physically, the girl appeared pale, rather bluish and without energy. On exertion there were breathlessness and cardiac palpitation. She was in good flesh and objectively there were no evidences of any ailment of the alimentary tract. The hemoglobin was 45%, r.b.c. 3,600.000, leucocytes 11,800. Blood films exhibited no atypic red cells, but there were many fragmented corpuscles. The fragility test revealed a ratio nearly double the normal. The urine was pinkish red, gave test for blood pigment but contained few red blood cells. A tube passed into the stomach secured more than 500 c.c. of almost carmine colored water fluid and a small quantity of food. This material gave positive blood pigment tests. All other clinical and laboratory tests were negative. The blood serum appeared pinkish. No spectroscopic observations were possible.

Explanation of "gastrorrhagia"—Chronic poisoning by volatile hydrocarbons (naphtha, benzene, xylol, etc.)—accompanied by intermittent blood lysis intravascularly—capillary dilatation and the appearance of laked blood in gastric contents and urine—toxic gastrorrhagia.

Change of occupation, blood transfusion and the feeding of high vitamin diet and cod liver oil restored the patient to health.

Case VI.—Male, aged 27, brought to the hospital in collapse. The evening previous to entrance, while the patient was reaching for the reins over the dashboard of a buggy, the horse became alarmed and kicked violently. The dash-board was smashed and the patient was struck in the epigastrium and knocked from the carriage unconscious. When he gained consciousness, he experienced excruciating epigastric pain and vomited large quantities of red blood. Under morphia, vomiting ceased and the patient became comfortable. However, frequently thready pulse, pallor, sighing respirations, with later shock, progressed rapidly.

The patient was comatose at examination, pale, cold and sweaty. There was a swelling in the epigastrium, and the upper abdomen exhibited board-like rigidity. While arrangements were being made to transfuse the patient preparatory to exploratory laparotomy, he expired.

Autopsy revealed a ragged tear in the anterior wall of the stomach, freely bleeding vessels and the peritoneal cavity partly filled with blood serum and clotted blood. Traumatic gastrorrhagia.

Case VII.—Male, aged 54 and weighing more than 250 pounds, had attended a Christmas Eve dinner at which he had not eaten very generously, but had partaken freely of alcoholics. Two hours after dinner he experienced acute knife-like agonizing mid-epigastric pain, and began to vomit, first food admixtures, and later great quantities of fluid and clotted blood. A diagnosis of "acute indigestion" was made, but the patient, even after vomiting was controlled, sank into shock rapidly and was brought to the hospital.

Examination revealed a heavy florid type individual, with shallow, stertorous respiration, cyanosis and cold, clammy extremities. The epigastrium was distended, and there was an indefinite mass palpable directly above the navel. There was begin-

ning rigidity of the abdominal wall. Gastric lavage returned large, liver-like clots. The heart tones were feeble, the rate frequent, the pulse thready, and systolic blood pressure, in spite of general sclerosis, barely 100.

A diagnosis of acute perforation of peptic ulcer, with involvement of the pancreas, was made. The patient died before midnight.

Autopsy disclosed gall-stones and acute hemorrhagic pancreatitis, the entire pancreas exhibiting apoplexy-like hemorrhages. Fat necrosis was extensive.

Case VIII.—A man aged 56 telephoned from an hotel, requesting a prescription to relieve his dyspepsia. He was informed that no treatment could be given unless he were examined. He refused examination, but later in the day again telephoned and requested to be given medicine to relieve what he called "sour stomach." He was refused, and told to present himself for examination. He finally did so, and when he appeared, seemed in pretty fair general shape except that he seemed somewhat pale and tired. He had had no pain, but on account of "sour stomach" had broken the journey on the way from Grand Rapids to his winter home in the south, believing that a short rest would prove beneficial.

Physical examination disclosed practically nothing except a rather noticeable fullness in the region of the stomach and a moderate pallor of the skin and mucous membrane. A stomach tube was passed with the idea of therapeutic gastric lavage. About three quarts of fresh blood, with moderate sized clots, were recovered. After the gastric lavage, local protective tenderness was elicited in the region of the duodenum. The patient gave a history of duodenal ulcer, and had recently been "cured" by the Leube-Sippy regimen in a hospital. (Later roentgenologic examination confirmed the diagnosis of duodenal ulcer).

Explanation of hemorrhage can be found in an acute recrudescence of a quiescent ulcer, with involvement of a fairly large artery in the base of, or adjacent to, the ulcer. The rapid filling of the stomach with blood may have been a means, mechanically, to control hemorrhage by pressure, particularly since this patient did not vomit.

Case IX.—A male, aged 44, who had been on "gastric ulcer treatment" for two years, suddenly experienced acute pain below the right rib edge, the pain radiating to the spine in the upper lumbar region. Associated with this pain was produced emesis of blood-stained food admixtures, and later bright red blood. There were no attendant shock and pain following the vomiting, but the patient's feeble pulse and dizziness resulted in his being brought to the hospital.

Physical examination disclosed an aortitis, an early cardiac dilatation, a palpable liver, and local tenderness in the right upper abdominal quadrant. After entering the hospital, the patient again vomited and the vomitus was made up wholly of fluid red blood.

A tentative diagnosis of non-obstructing duodenal ulcer was made, and the patient treated accordingly by rest, starvation and blood transfusions. He made an uneventful recovery. The Wasserman test later was shown to be positive. Roentgen examination indicated a thick-walled stomach (cirrhosis?) and a duodenal deformity, evidently an ulcer.

Explanation of hemorrhage appears to lie in acute rupture of a sclerotic arteriole in the base of an ulcer, whose mucosal surface previously had been protected by scar.

Case X.—A full-blooded male, aged 25, who had taken several "cures" for "gastric ulcer" and who apparently was in excellent health, strength and comfort, late at night, suddenly experienced acute right upper quadrant pain and rapidly sank into a semi-comatose state.

When seen he was in shock and there were evidences of an effusion into the upper part of the greater peritoneal sac. Exploratory laparotomy disclosed a stomach full of clotted blood (there had been no vomiting) and a duodenal ulcer which had perforated into the peritoneal cavity; a small spurting arteriole was present toward

the old ulcer base. Dr. Ralph Kordenat treated the perforated ulcer by suturing and enfolding and performed gastroenterostomy. The patient made an uneventful recovery.

Case XI.—A man, aged 72, came from Montana to Chicago to attend the stock show. Shortly after his arrival, without warning and without pain, he began to vomit large quantities of red blood, and was hurried to a hospital. He gave a history of having been treated for "gastric ulcer" forty-two years previously, and since that time, had been in excellent health.

Abdominal examination revealed nothing abnormal. The patient was in fair flesh, but rather pale, and was a marked arteriosclerotic. Blood pressure (even after much bleeding) was systolic 182, diastolic 110.

Bleeding could not be controlled by ordinary means, so the patient was explored. A thick callous plaque-like ulcer occupied the posterior wall of the duodenum, about two inches distal to the pylorus, in which space there was found a bleeding artery. A modified Heineke-Mikulicz, with gastroenterostomy, was performed. The patient made an uneventful recovery.

The interesting features of this case were the long period of quiescence of an old ulcer, the general arteriosclerosis and the reappearance of almost fatal bleeding in an ulcer so many years after ulcer dyspepsia in early life.

Case XII.—A male, aged 58, came from the Michigan Peninsula on account of dyspepsia of ulcer-like type. Three years previously, he had had a gastroenterostomy performed at a large clinic for duodenal ulcer. Following the gastroenterostomy, during the succeeding two and one-half years he had experienced three very severe hemorrhages, with bloody emesis and pronounced melena. During the past month a dyspepsia of mild retention type had been present, and the patient has felt unaccountably weak and restless.

At examination of the abdomen, there was a finger-like ridge palpable above and to the right of the navel. It was slightly tender to pressure. The stomach seemed somewhat dilated. The stool contained four plus blood by the benzidin test. Within a few hours after the patient was first seen, he had severe right upper quadrant pain and vomited much blood. Exploratory laparotomy, under local anaesthesia, was performed, and a mass as large as a lemon occupying the first portion of the duodenum was revealed. The stomach and jejunum were filled with clotted blood. The gastroenterostomy stoma was wide open. The pancreas was firm, and there were enlarged lymphnodes above the pylorus. Involvment of the pancreas prevented surgical removal of the pyloric tumor. For three weeks, the patient bled almost constantly: hemorrhages could not be controlled by transfusion, starvation, rest or other agents. Symptoms of colon obstruction appeared, and a second abdominal exploration was made with the object of performing colostomy. The pyloric tumor which previously had been as large as a lemon had grown rapidly, involving not only the pancreas, but the liver and the transverse colon near the hepatic flexure. The mass had perforated into the colon. The patient died thirty-six hours following the second operation.

The interesting features of this case are a duodenal ulcer, whose progression apparently was not halted by gastroenterostomy; the extension of the duodenal ulcer to the pylorus, with later malignant transformation at the gastric edge of the ulcer; the frequent hemorrhages (after gastroenterostomy); the rapid extension of the tumor mass with early involvement of adjacent viscera.

Etiology—From the above case briefs, it will be recognized that since the pathology and functional disturbances concomitant with the appearance of blood in the vomitus or the stools are of various nature, an adequate conception of matters is essential before management is considered. Sudden, copious bleeding from the stomach is commonly the result of accident or is a complication of a previous lo-

cal, general or constitutional ailment. It may be so acute and extensive as to prove rapidly fatal (about 2% in primary gastric bleeding). Moderate or abundant hemorrhages may occur at frequent or infrequent intervals. There is often a peculiar tendency to recurrence. The quantity of blood lost at each occasion may vary greatly in a given case.

Seepage or "occult" bleeding from the stomach is generally associated with primary progressive pathologic changes in the gastric mucosa, or is a secondary local manifestation of a systemic or constitutional fault.

In the different types of gastrorrhagia, the histo-pathologic condition of the stomach mucosa varies from simple, capillary congestion associated with local or general rupture (or diapedesis?) of minute capillary net works, to extensive loss of surface epithelium with destruction of the layers of the stomach wall and the erosion of large blood-vessels. Either process may begin intramurally, in which event the mucosa first suffers, or extramurally, when the blood vessels primarily are attacked. There is a type of gastrorrhagia which periodically occurs in females, in definite relationship to the menstrual cycle, where copious hematemesis is associated with no demonstrable gastric pathology. In the hematemesis accompanying certain anemias, infectious ailments, acute and chronic systemic toxic states or following operations upon intra-abdominal viscera other than the stomach or duodenum, there may likewise be no grossly apparent injury to the stomach mucosa.

Gastrorrhagia is associated with hematemesis or melena, or both, as follows:—

(a) In primary gastric disease, acute or chronic gastritis, simple or phlegmonous, acute gastric erosion, acute or chronic benign ulcer, ulcus carcinomatosum, carcinoma, sarcoma, syphiloma, tuberculoma, polyposis, ulcerated gastric cirrhosis, varicosities or aneurysm of intrinsic gastric arteries or intramural parasite (echinococcus, nematodes).

(b) In conjunction with chronic disease of the heart or blood vessels.

(c) Complicating chronic disease of the liver or gall-bladder or ducts (cirrhosis, neoplasm, portal thrombosis, Banti's disease, cholelithiasis, cholecystitis).

(d) Disease of the spleen (chronic splenitis, leukemia, Gaucher's spleen).

(e) Malfunction of the pancreas (acute and chronic pancreatitis).

(f) Toxemias associated with ailments of the kidney, central nervous system, thyroid gland, adrenal, hemolymph nodes.

(g) Bacteriemias or protozoemias (typhoid fever, smallpox, measles, malaria, yellow fever, cholera).

(h) Chemical poisons (phosphorus, hydrocyanic acid, volatile hydrocarbons, split-proteins and their products), and probably following burns upon the body surface.

(i) Local injury: (1) Trauma from falls, foreign bodies, blows, crushing injuries or stab wounds; (2) poisons introduced by mouth.

(j) Disordered blood states: Hemophilia, purpura, chronic anemia ("sec-

ondary" or "pernicious"), acute or chronic cholemia.

(k) In connection with certain neuropathic states, as hysteria, angioneurotic edema, tabetic crises, epilepsy, progressive paralysis.

(l) In association with physiologic cycles of females, as the catamenia and climacteric.

(m) Following operations upon organs other than the stomach, particularly when such operations are intraperitoneal.

(n) Blood may enter the stomach from a diseased lung, esophagus, adjacent viscus (duodenum, jejunum or colon by fistula) or great vessel.

Morbid Anatomy in Gastrorrhagia—Gross or microscopic alterations in the stomach wall bear out an irregular relation to the quantity of blood present in the viscus, vomited or passed by the bowel. Abundant, even fatal hemorrhage may occur and yet no visible cause of such can be demonstrated in the mucosa. This phenomenon may exist where profuse bleeding is associated with infectious disease, cirrhosis of the liver, surgical operations not on the stomach, hysteria, burns on the surface of the body, blood dyscrasias or traumata to the abdominal wall. Commonly, however, gastrorrhagia occurs in connection with some type of peptic ulcer, or carcinoma, and in such ailments fissures, granulating ulcer edges or necrotic tumor areas can be noted in more or less definite relationship to blood-vessels.

After severe hemorrhage the stomach mucosa appears pale, yellowish-pink, often with scattered areas of reddish-brown mottling in the mucosa and submucosa. Some grade of general edema is present. The mucosa dries rapidly when exposed to the air and then has a smooth, shiny appearance. The rugae are indefinite and the gastric wall is flabby and inelastic. When peptic ulcers bleed profusely or intermittently, local destruction of the stomach wall with perforation, protected or not protected by peritoneal adhesions, is not an uncommon occurrence. Of ulcers bleeding copiously in a series of 185, at operation or autopsy, 42% revealed perforation, actual or protected. In acute, profusely bleeding ulcers, tissue necrosis may take place rapidly, peritoneal protection is impossible and perforation may occur even before hematemesis or melena occurs. The symptoms and signs of the perforation may mask those of severe hemorrhage. At laparotomy, the stomach may be seen to be filled with clotted blood and food, while between the coils of the intestines, or in the peritoneal sacs may be found blood clots, serous fluid or pus.

Seepage of blood into the stomach is most frequently noted in connection with granulating ulcer edges, ulcerating, necrosing cancer, in achylias, primary as result of chronic atrophy of gastric mucosa, or secondary to idiopathic anemias, blood disorders or extra-gastric malignancy. With exception of the achylias, the mucosa is generally edematous, congested and bleeds readily on handling. In the achylias, the mucosa is often thin, pale and smooth. If it is scraped with a knife a pale, reddish-brown fluid can be collected, which chemically or phys-

ically can be proved to contain blood pigment.

Signs and Symptoms of Gastrorrhagia — (a) — *Hematemesis* — Sudden vomiting of large quantities of blood may occur without noticeable premonitory symptoms or previous evidences of disease. The vomited blood may be bright red and fluid. It is commonly mixed with undigested food and mucus. Clots may be present. They usually occur toward the end of emesis or when the blood has lain in the stomach for a time before being vomited. In general, the higher the gastric acidity the larger the clots. When the acidity has previously been low or where hemorrhage has neutralized free hydrochloric acid, coagula form relatively slowly. The quantity of blood vomited varies greatly in different patients or in the same individual at different times. The hematemesis may not represent the extent of the gastric hemorrhage. A cupful may be vomited and yet the stomach remain filled with free or partly clotted blood, which is later passed by the bowel or washed from the stomach. Such condition often leads to a sense of false security. Clots in the gastric lumen may temporarily stop hemorrhage or may mask a gradual but persistent bleeding, which, subsequently, as a result of error in diagnosis or treatment, may prove fatal. Enormous hematemesis sometimes occurs. One of our patients vomited nearly eight quarts of free and clotted blood.

Slow seepage of blood rarely precipitates hematemesis. In such instances vomiting may result from other causes. When this happens the vomitus may be colored reddish-tan, brown or even black. In advanced gastric carcinoma or in pyloric obstruction caused by an eroded ulcer, such vomitus is not uncommon.

(b) *Melena*—Practically in all instances seepage of blood from the stomach and nearly all cases of profuse gastrorrhagia are accompanied by stools more or less colored with blood or blood pigment. Where rapid loss of blood occurs, the stools may be bright red and mixed with clots. Commonly, however, the stools are dark brown or slate black. Not infrequently, abundant hemorrhage from the stomach may be unaccompanied by hematemesis, but melena may be observed either within a few hours of other clinical evidences of internal bleeding or after an interval of a day or more. Unless stools are carefully scrutinized, such hemorrhage may be overlooked, with the possibility of serious consequences.

Where seepage of blood occurs the stools may be but slightly altered in gross appearance, and unless search for blood pigment be made in the laboratory, the existence of an "occult" gastrorrhagia may remain unsuspected.

Tests for "Occult" Hemorrhage— In retention of stomach contents, positive "occult" blood tests are not rarely returned from the food contained therein. In such an instance, it can be seen readily that the test has no clinical value—namely, the positive tests may be due entirely to retained food in the absence of a gastric lesion, or it may be due both to a bleeding gastric lesion and to the food admixture. Similar observations apply to the making of "occult" blood tests upon stools. It is

quite necessary when making chemical tests for blood pigment in feces, to be sure that positives are not due to food stuffs or medicines (iron compounds).

Stools passed during the menstrual period are not infrequently mixed with blood. This should be appreciated particularly in the examination of stools from females.

Examination of Feces—For blood or blood derivatives, an analysis of stools is of considerable value to both internist and surgeon. If the analyses are not intelligently made, then the facts returned are clinically of little worth. In surgical disease of the stomach and duodenum the significance of certain special tests should be emphasized. It is not always absolutely necessary to perform some of these tests in order to arrive at a diagnosis of the ailment under investigation, but it cannot be denied that the routine performance of these analyses not only at times gives information impossible to obtain in any other way, but conveys a clearer conception of alterations taking place at the site of the disease.

Methods of Examination—Excepting in special instances (after severe acute hemorrhage or other emergencies) proper preparation of the patient should precede stool examination. As routine, all forms of medication should be interdicted during the time that specimens of stool are collected. Unless this caution is remembered the stool examination may be useless. Harmful deductions may be derived from the result of laboratory tests.

Demonstration of Altered or "Occult" Blood in the Stools.—The patient's intestinal canal should be first completely emptied by stoppage of food ingestion and where safe, by the administration of 2 ounces of *oleum ricini.* Any diet given should be free from meat products or an excess of green vegetables for two days. On the third day nothing but milk or cereal gruel should be given. On the morning of the fourth day, a saline cathartic should be administered, and the second stool passed, collected and sent to the laboratory in a covered vessel for analysis.

Tests for "Occult" Blood.—Numerous tests are in vogue. If the stool has been properly collected and the tests carefully performed, they are practically all of equal worth clinically. On account of abortive reactions, not infrequently given by the use of poor preparations of aloin, guaiac or phenolphthalein, routinely it has seemed to me that benzidin solutions have returned the most reliable information. The pinkish-gray powder should be used, and this should be kept in a brown bottle, carefully stoppered.

Interpretation of Positive "Occult" Blood Tests.—A positive response to chemical test for blood in the stool signifies only that there is a bleeding point somewhere between the lips and the external anal ring. It is thus evident that tests should be rigidly controlled and interpreted strictly in relation to the clinical history of the case. Positive tests are commonly *constant* in malignancy. They are *intermittently* present in the stools from chronic recurring peptic ulcers.

The *negative test* for "occult" blood in feces is of aid in excluding malig-

nancy, particularly in instances where, with a dubious clinical history, an atypic, abdominal tumor can be demonstrated.

We have not found the so-called string test, suggested by Einhorn, of reliable or of any practical value. It was positive in less than 10% of 230 proved peptic ulcers. Such clinical toys are a waste of time and effort.

Systemic Evidences of Bleeding.—If the hemorrhage has been of small quantity, there may be but slight physical evidences of such. Where a large amount of blood has been lost in a short time, pallor, cold clammy skin, sighing respiration, with or without rapid pulse and dilated heart, are usually evident. Frequently fainting occurs. In some instances there is delirium. The temperature is usually subnormal at first, but in fatal cases there may be an abruptly developing hyperpyrexia before death. Gastric hemorrhage is not infrequently accompanied by severe abdominal pain. Unless the hemorrhage has been sudden and severe, the discomfort produced by the pain may mask the clinical evidences of threatened shock and collapse. Patients not uncommonly suffer extensive hemorrhage without hematemesis. The blood may pass into the bowel and remain unrecognized. In these patients, shock, collapse and death may occur without the underlying causes being discovered until laparotomy or autopsy be performed. All too often, one reads newspaper accounts of death from "acute indigestion" in this class of case. In a chronic dyspeptic or in the course of an acute attack of abdominal distress, the appearance of anemia and shock should always indicate hemorrhage until the signs and symptoms are proved to be due to other causes.

Where hemorrhage complicates the actual perforation of such gastric lesion as ulcer or cancer, the development of perigastric abscess, a general peritonitis or fistula may cloud the diagnosis.

Prognosis—About two per cent of instances of gastrorrhagia are acutely fatal. Oft-repeated hemorrhages occurring with a brief interval raise the total mortality to about five per cent. Sometimes the hemorrhage itself is not fatal, but death is caused as a consequence of the lighting up of infection, by a perforation with peritonitis or by heart or kidney failure.

Management of Gastric Hemorrhage—The clinical cases cited in this report make it evident that management of gastric hemorrhage, in order to be successful, depends upon an accurate appraisal of the condition responsible for the initiation and maintenance of the hemorrhage. Particularly does this apply with respect to operative procedures contemplated toward the abdominal viscera.

First, a brief history of the patient's past and present constitutional and digestive difficulties should be obtained —preferably not from the patient (except in emergencies) but from attendants or relatives. Commonly this can be done while the patient is being placed in bed or taken to a hospital. Without loss of time, especially when lesions of the abdominal viscera are known to exist or are suspected, a

hypodermatic injection of one-fourth to one-half grain of morphine sulphate with or without atropin should be made. Where hemorrhage is copious and there are marked retching and vomiting or when a patient is restless and noisy, there is no drug so valuable as morphine in physiologic doses in the emergency treatment of hemorrhage—it lowers blood pressure, slows the heart, relaxes muscles systemically and locally, quiets restless or hysterical patients and assures complete bodily rest. Much larger doses than are commonly given should be employed—even up to a half to a grain every two or three hours for several doses. The main contraindication to the exhibition of large or frequent doses of morphine is slowing of the respiration to 10 or less per minute. When morphia is given frequently, atropia should be used cautiously or omitted. The too frequent exhibition of atropia results in diminished urine output or even anuria and the attendant dryness of mucous surfaces and skin are distressing to the patient.

It is not necessary to emphasize that the patient should be put to bed, and kept there, external heat being supplied liberally and the central nervous system stimulated by the head and shoulders being low. This can be accomplished by elevating the foot of the bed on ten-inch blocks. This position not only favors normal cerebral circulation but permits vomiting without effort and prevents regurgitation of vomited material into the bronchi. Particularly is regurgitation avoided if patient is inclined on to the left side and the head placed low and turned to the left.

After this initial treatment has been instituted, with the patient stripped, there should be carried out, in every instance, a rapid physical examination, no part of the body from the head to the toes being neglected. Such examination commonly gives indication as to the source of bleeding: whether hemorrhage has resulted from venous stasis, concomitant with heart malfunction, from liver cirrhosis, pulmonary lesions, anomalies of the spleen, biliary tract and pancreas, abdominal trauma or intragastric or intra-intestinal lesions. In all instances, whether or no an abdominal focus of disease is located or suspected, the patient or his relative should be questioned with regard to the hemophilic taint.

The blood pressure always should be taken, not only to secure a relative appraisal of deficiencies of heart strength and blood volume, but in order to establish a point from which subsequent blood pressure readings may be contrasted in patients who go into shock or continue to bleed.

Should the patient be in a hospital, complete blood counts should be made immediately and the blood clotting time estimated by such reliable procedure as that of Thomas Boggs.

If vomiting is copious, and particularly if it is accompanied by much retching and the appearance of large blood clots, then by means of a large bulb-free stomach tube, thorough lavage should be performed with normal salt solution at a temperature of 110° Fahrenheit, as suggested by the late Dr. Rodman. This procedure is remarkably efficacious in stopping hemor-

rhage and putting the stomach at rest. So long as large clots are in the stomach, peristaltic activity will continue in an effort to get rid of or digest them. Such mechanical activity on the part of the stomach interferes with protective clot formation at the site of intragastric bleeding. The heat of the lavage solution acts an an admirable hemostatic agent. In cases of actual or potential perforation, the emptying of the stomach lessens the danger of peritoneal contamination by free food residues and blood. Where frank perforation has existed, free lavage after Rodman's method, with the patient in a partial Trendelenberg position, rapidly empties the stomach and renders subsequent operative procedures less hazardous. Our experience with lavage by heated solutions in patients exhibiting gastric hemorrhage is extensive: we have never observed any harmful effects. In many instances, it has seemed that lavage after this fashion served as a life saving measure.

Topical applications to the abdomen. Many years ago, I abandoned the routine application of ice-bags and ice water-coils to the abdomen in patients where hemorrhage was suspected of coming from gastric or duodenal lesions. In our opinion and from our clinical experience, the local application of ice is detrimental: it chills an already shocked patient, systemically as well as locally; it lowers body temperature and interferes with adequate central nervous system function; it has relatively little, if any, effect toward "constricting" blood vessels or capillaries and thus lessening bleeding —in fact, quite likely continued cold applications paralyze the vascular neuromuscular mechanism and by preventing normal constrictor action, prolong a hemorrhage which otherwise might cease spontaneously. One has but to scratch his hand and place over the bleeding scratch a piece of ice in order to prove how long bleeding continues following cold applications. Only in instances where physical examination indicates that perforation actually is taking place or has occurred and the peritoneum has been subjected to mechanical or infectious traumata, do we employ cold abdominal applications. In such circumstances they are used in an attempt to immobilize a part and to lessen peritoneal engorgement. Frequently such measures permit limitation of an inflammatory process to such extent that later, at an opportune time, abdominal exploration may be performed safely.

For years, I have favored extremely hot moist applications over a suspected bleeding focus. Usually these applications were employed as hot compresses rather tightly bound upon the abdomen and frequently renewed. The tight fixation of the compresses limits the motion of the abdominal wall and lessens visceral peristaltic activity. The heat prevents shock; possibly it has a derivative action upon the capillary bed and if the compresses are sufficiently hot and moist, stimulates blood coagulation. The advantage of heat over cold as an agent toward improving the patient's feeling of well being, is self-evident.

Food.—Mouth feeding in all its aspects should be strictly interdicted. So long as the patient is ingesting mate-

rial into his stomach, gastric peristalsis is stimulated, and with this stimulation of peristalsis, permanent clot formation is attained with difficulty. The sucking of ice, the drinking of ice water, the administration of such hemostatic agents as adrenalin solutions (liquid, gelatine or otherwise) or the effort to improve nourishment by exhibiting gruels, soups or so-called "ulcer diets" can be productive only of harmful effects. An empty stomach rapidly becomes peristalsis and secretion free, and if the viscus remains empty for longer than twelve hours, muscular contraction of the wall mechanically compresses bleeding capillaries or arterioles and lessens or completely stops hemorrhage. All too often, attempts at feeding or to administer medicinal and dietetic ulcer regimes initiate or prolong emesis and aggravate the local pathologic condition responsible for hemorrhage. If bleeding is due to such local pathology as peptic ulcer, and if hemorrhage has been repeated or is continuous, one must recall that perforation is a strong possibility; hence attempts to administer food or medicine by mouth are a potent influence toward precipitating perforation. This observation can be substantiated readily by a short residence at any busy gastroenterological or surgical clinic. There is no doubt that many patients who succumb suddenly to "acute indigestion" are instances where the cause of death is acute perforation of an ulcer or cancer; and this most serious accident would have been avoided had "routine" ulcer treatment orders, so common to many hospitals, *not* been carried out. It is our practice not only *not* to administer water, food or therapeutic agents by mouth during the progress of gastric hemorrhage, but to interdict anything but small sips of very hot water for at least four days after definite proof is available that hemorrhage has ceased and that the local abdominal examination indicates that peritoneal involvement is not present.

Nourishment for the first few days of gastrorrhagia, unless the patient is in extremely low general physical condition, is not especially needed, provided measures are directed to maintaining body fluids. McVicar and others have shown how essential it is that body fluids which are lost by hemorrhage or by persistent vomiting be replaced, if one is to avoid toxic crises. We have never hesitated early to increase the fluid content of the body by all known available routes; intravenously, subcutaneously or per rectum. Commonly, sufficient fluid can be given per rectum by the Murphy drip to replace fluid lost by bleeding, to prevent renal stagnation, to keep moist the mucous surfaces, particularly of the mouth and to counteract shock. For more than ten years, we have employed as a nutrient enema the following: 8 ounces of normal salt solution; 50 c.c. of glucose syrup and 30 cc. of 50% alcohol. This is administered, at body temperature, and by the Murphy drip. The whole quantity generally is given four times within twenty-four hours. Medicinally, agents such as atropine, bromide, morphine, digitalis or even calcium may be added to these *enemata* with beneficial results. Where the blood

coagulation time is delayed, and bleeding, particularly profuse seepage of blood, occurs, we do not hesitate to give intravenously several times during twenty-four hours, 500 c.c. of one per cent solution of sodium bicarbonate and 20 c.c. of five per cent calcium chloride. Where the patient seems to be in poor flesh, in addition to being dehydrated, the sodium bicarbonate solution is supplemented by glucose in the proportion of approximately two per cent. In instances where rectal feeding is poorly borne and where it is difficult to administer fluid intravenously, normal salt solution can be administered at convenient places, subcutaneously, in large quantities, provided local tissue pressure from administered fluids is avoided.

Mouth-feeding should only be begun when there is conclusive evidence that hemorrhage has stopped and has not recurred. An increasing blood pressure, a faulty pulse rate whose quality is improved, a stationary or increasing red blood count and hemoglobin estimation are sufficient clinical evidence that hemorrhage no longer continues. These, especially, if the patient exhibits physical well being, is free from pain or nausea and has a flat, soft epigastrium. "Occult blood tests" may be positive in the stools for many days after hemorrhage has stopped on account of retention, and if mouth feeding is interdicted until occult blood tests are negative, then the patient is quite likely to have his resistance greatly reduced by lack of food, but, what is more important, to have his body fluids diminished below the safety point.

It is well not to feed by mouth until two days following cessation of hemorrhage. When mouth feeding is begun, then a few simple but fundamental principles should be followed: Food should be administered in small quantity frequently and, to avoid gastric spasms, should be given warm; foods which do not stimulate acid secretions should be chosen, namely, carbohydrate mixtures in preference to mixtures of protein (milk, eggs, etc.); all foods should be selected with the idea of their leaving the stomach almost immediately, in order not to excite peristalsis or locally to traumatize an injured area. One should be sure that the vitamin content of the food administered is adequate. This has been emphasized frequently by Seale Harris.

It is our policy to give milk in no form except where it is citrated or parboiled: Raw milk results in tough casein clots, and these clots excite the stomach to effort, both secretory and muscular, just as strenuously as if the patient were given meat to eat. If milk be used at all, it should be parboiled or mixed with an equal quantity of barley water, in order that small flocculent casein clots result, or to each ounce of milk one gram of sodium citrate should be added. Personally, I prefer to use very little milk or milk mixtures. Generally, our feeding routine is two ounces of water gruel (made from barley, farina, cream of wheat, oat meal, etc.), every hour, and at alternate hours an ounce of sweet fruit juice. After the first twenty-four hours, to the water gruels may be added thin custard or strained

soups, made particularly from fresh vegetables. This feeding supplies adequate vitamin demands, is readily borne, does not excite peristalsis or stimulate secretion, and its caloric value can be so computed that the patient can be built up rapidly from 400 calories to 1200 calories daily. This quantity is quite sufficient for the average individual in bed at rest. When the feeding demands are increased, then thin cereals, purees from potato, peas, beans, carrots and other vegetables and small quantities of chopped meat, particularly liver, kidneys, sweetbreads and calves' brains may be exhibited. For at least two weeks following a hemorrhage, one should be sure that the calories are kept below 3000, and that at least six feedings daily are given. Charts of pulse, temperature and blood pressure should be kept, in order that one is reassured that bleeding has not recurred. If the patient is in a hospital, certainly the hemoglobin and the blood count should be estimated every other day.

Even after the patient has gained strength and energy and is up and about, for months he should be cautioned against an excess of protein or fat (the fat slowing the emptying rate of the stomach) and should avoid "roughage feeding" in every form. After the first or second hemorrhage, patients frequently gain weight very rapidly. This should not be allowed, inasmuch as should an acute emergency arise from another hemorrhage, with or without perforation, the operative risk upon an obese individual is very grave.

Particularly to individuals who have had hemorrhage from a bleeding gastric or duodenal ulcer, definite information regarding the nature of the ailment and its possible consequences should be given. It should be emphasized that a patient who has had one severe hemorrhage is likely to have another, and that each succeeding hemorrhage is likely to be more severe. Furthermore, the anatomic consequences of hemorrhage should be mentioned—namely, that with each succeeding hemorrhage there is a greater destruction of the gastric or duodenal wall and that it is not possible to tell when this destruction will advance to the stage where the wall of the viscus is completely destroyed and perforation result. It has always been my custom to tell a patient who has had one severe hemorrhage that he is potentially a subject for surgery. No physician is able to determine in any given patient whether or no he will have another hemorrhage, or how soon there will be a recurrence of hemorrhage. Neither is a physician able to tell in any given case the consequences of hemorrhage—whether a long uncontrollable "spurter" will be opened, whether perforation will occur immediately or within a short time or whether the extension of the ulcer will involve to a dangerous degree an adjacent viscus. In the circumstances, it is only fair to any subject that the true condition be explained to him, and, provided the bleeding does not result from a blood dyscrasia, or during a physiologic cycle such as the menopause, or in association with a disease not definitely ascribable to the stomach or duode-

num, surgical exploration and treatment should be insisted upon. Frequently, such course of management is refused by the patient, but if the physician has made his viewpoint clear and the patient understands it and is willing to assume the risks, then the physician is relieved of much responsibility in the carrying out of any regime other than surgical. It is astonishing how frequently, however, both patient and physicians are readyto gamble upon the future, when the patient has already experienced one severe gastric or duodenal hemorrhage. While this may be human nature, yet when crises occur, the patient who is turned over for surgical management is in a far more hazardous state than he would have been had surgical intervention occurred at a time when the patient's general condition was excellent and what had to be done surgically could have been carried forward in a leisurely and scientific manner.

The stoppage of bleeding by drugs has not, in my experience, been very successful. This is probably due to the fact that I have not employed many drugs for such purpose but rather, by keeping the patient at rest in bed, stopping peristalsis by morphia, supplying sufficient fluid to stimulate cerebral activity and keeping the stomach free from food, etc., I have not had to employ many of the commonly administered local hemostatics. Not rarely, one hears of good results following the introduction into the stomach of such mixtures as adrenalized gelatin, adrenalin solutions, tannic acid solutions, etc., etc. The use of adrenalin intramuscularly or the intramuscular administration by the hypodermatic route of coagulating agents such as thrombo-plastin, coagulose, horse serum, etc., has been favorably recommended. Certainly, if these agents are not administered in such quantities as to produce harm, one may employ them on the general theory that they may do good, or that, if the case should turn out badly, these agents having been administered, the physician's conscience is clear, inasmuch as he has exhibited all known remedies to prevent a catastrophe. However, no one yet has shown just how much of the above agents it is necessary to give to any individual or to any group of individuals, in order to stop gastric or duodenal bleeding, whether that bleeding be due to seepage or to free bleeding from an arteriole or an artery. Further, I have always felt that the administration of the above mentioned agents leads to a sense of false security, and that while these agents were being pumped into the patient, bleeding was progressing to the point where serious loss of blood might take place or the continued bleeding extend such lesion as an ulcer to the stage of fatal perforation. In my experience, the most potent agents to stop bleeding when the bleeding was not from a "spurter" have been the intravenous administration of 20 c.c. of five per cent calcium chloride solution every two hours for six doses, or, better still, prompt transfusion of large volumes of whole blood after the method of Kimpton, Brown-Percy. If these agents do not stop bleeding within thirty-six to forty-eight hours, it is evident that one has to do with a condition where it would

be wise to urge surgical exploration without delay. Such exploration may reveal a bleeding malignant ulcer, an arteriole dripping constantly, or an artery from which an obstructing blood clot is frequently dislodged.

It has been advanced by individuals, quite carelessly and without clinical or laboratory proof, that blood transfusion tends to prolong hemorrhage by increasing blood pressure or by dislodging clots from the mouths of arterioles or arteries or by both. In a rather extensive clinical experience, I have never seen any ill effects following the massive transfusion of whole blood; but I have seen instances where neither blood transfusion nor any other measure permits the formation of an obstructive clot at the mouth of a "spurter" of fair size. The opinions which have been advanced regarding how much massive whole blood transfusion (and I speak of "whole blood" transfusion because it has never been our policy to use citrated blood or blood altered in any other manner) increases blood pressure or dislodges clots, have been repeated by one clinician after another, without there seeming to have been, so far as I can learn, any basis of fact for these opinions. In order to learn definitely just what effect increase in blood volume or increase in blood pressure has upon a freely bleeding vessel, at my suggestion, my associate, Dr. Ralph A. Kordenat, carried forward a series of experiments which he will report in detail later, but from which he has permitted me to make certain statements. Working with fairly large dogs at the Research Laboratories of the University of Illinois, Dr. Kordenat and his associates exposed arterioles and arteries, severed them and permitted free bleeding and subsequent clot formation at the mouths of the vessels. The intravenous introduction of fluid in quantity almost to "water-log" the dog did not dislodge the clot, nor did the hemorrhage recur when the blood pressure had been raised, mechanically or by the use of adrenalin, to more than double the normal blood pressure. Furthermore, quantities of fluid, intravenously introduced and comparable in proportion to body weight or to the animal's normal fluid content, added to such amounts of blood as would be introduced during a therapeutic transfusion, resulted in but a very slight and transient rise in blood pressure, and had no effect whatever with respect to producing a recurrence of hemorrhage. These experiments, conducted by Dr. Kordenat and his associates, would seem to be of the greatest importance in demonstrating the harmlessness of whole blood transfusion as therapeutically carried out in the control of visceral hemorrhage, and should be of great assurance to physicians in their proceeding to transfuse promptly and frequently individuals whose visceral hemorrhages are not controlled by general and visceral rest. These experiments substantiate completely our clinical experience with regard to therapeutic transfusion of whole blood, and also the intravenous exhibition of saline solutions and calcium chloride.

Persistence of visceral bleeding usually indicates pathology that war-

rants surgical exploration. Too often, patients are permitted to die from exhaustion, shock or anemia, because bleeding is allowed to continue interruptedly, while futile efforts, therapeutically or dietetically, are being made to stop hemorrhage, nourish a patient or "build up the blood." As I mentioned above, should an increasing pulse rate, a falling blood pressure and a falling blood count and hemoglobin estimation continue, the patient should be explored by a competent surgeon while he still is a fair surgical risk. Not infrequently, a persistently bleeding ulcer can be excised or enfolded, a "spurter" ligated or a small malignant ulcer excised, largely under local anaesthesia, and within a few days the patient is past danger and has a fairly reliable future ahead of him. Furthermore, this prompt action not rarely prevents perforation and fatal hemorrhage or peritonitis.

Thus far, I have not mentioned the use of the *x-ray* as an aid in determining the pathology responsible for gastrorrhagia. Purposely I have not mentioned the x-ray, hoping that it would be self-evident that x-ray investigation had little place in the locating of pathology productive of gastrorrhagia. Certainly, in acute hemorrhage or in persistent seepage, one should endeavor to forget that the x-ray method of investigating the alimentary tract had ever been devised. Every year it has been my misfortune to observe individuals who have experienced acute gastric hemorrhage and upon whom, even while bleeding persisted, the x-ray method of investigation has been employed. In many of these patients, the heavy barium mixtures have not only prolonged hemorrhages and made them more severe, but in numerous instances the consequences have been fatal on account of resultant perforation. It is our policy never to x-ray a patient by means of barium mixtures until at least four weeks following proof of cessation of a severe hemorrhage. Even then, one should proceed cautiously with both the fluoroscopic and the plate studies. Certainly, the use of the x-ray method while a patient is still bleeding subjects the individual to hazards which no roentgenologist or clinician should be willing or anxious to assume. For the guidance of house officers in all hospitals, there should be displayed prominently cautions that individuals who are brought into the institutions during gastrorrhagia or in whom gastrorrhagia appears, should not be x-rayed without the written permission of their chiefs. If, from clinical history, physical examination and the various simple laboratory tests which have been outlined above, a workable appraisal of the condition to be treated cannot be made, certainly, little of value will be added to the picture by roentgen studies, and most assuredly the patient will be subjected to risks out of all proportion to any information which may be gained.

Experiments With Phenylhydrazine

I. Studies On the Blood*

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SINCE 1918, when Eppinger and Kloss (1) first introduced phenylhydrazine in the treatment of polycythemia vera, an increasing number of reports from the clinical standpoint have been recorded, notably those of Owen (2) and Brown and Giffin (3). Notwithstanding the excellence of these reports, certain fundamental questions in connection with the effect of the drug remain unanswered. This is due to the difficulty of keeping in touch with patients over long periods and more particularly to the impossibility of subjecting them to the rigid research methods which can be conveniently carried out on animals.

The experimental work on animals has so far been directed largely toward the study of the effect of phenylhydrazine on the erythrocytes, and the chemistry of the blood. The effect of hydrazine compounds other than phenylhydrazine has been noted in experimental work on the liver. Investigations of the effect on other vital structures, particularly the kidneys, bone marrow and spleen, have been negligible as have studies on the effect of the total and differential leukocyte count. Moreover, too much attention has been paid to the toxic effects and pathologic changes due to phenylhydrazine and allied compounds, and far too little to the dosage used to produce these changes. Wells (4) has been widely quoted as having demonstrated fatty degeneration of the central cells of the hepatic lobule, but he used 0.1 gm. of hydrazine sulphate (not phenylhydrazine hydrochloride) for each kilogram of body weight in a single dose, an enormous amount as compared with the therapeutic dosage of phenylhydrazine. Other hydrazine compounds have been more extensively studied than phenylhydrazine itself, and conclusions with regard to the

†Bibliography for Studies I and II given at the end of Study II.

*Abstracted for Proceedings of the Staff Meetings of the Mayo Clinic, 1927, ii, 154-156.

The material in this paper was presented in a thesis by Edgar V. Allen to the Facsity of Minnesota in partial fulfillment of ulty of the Graduate School of the Univerthe requirements for the degree of M.S. in Medicine, 1928.

toxicity of phenylhydrazine have been drawn from these studies. That this is unjustified is evidenced by the fact that these compounds have diverse effects; for example, the absence of erythroclastic action after the administration of hydrazine sulphate.

In this study we have regarded compounds allied to phenylhydrazine as foreign to our problem and have limited investigation to the effects of phenylhydrazine administered in a manner comparable to its use clinically. Dogs have proved to be excellent animals for this purpose. The amount of the drug given to these animals in a period of five months of active treatment is equal to that given clinically in a period of from four to six years. This has permitted us, in a comparatively short time, to study the effects of experiments that would otherwise be prolonged. The specific information sought in these experiments is as follows:

The general effects of prolonged administration.

The effect on the erythrocytes of large but sublethal doses.

The effect on the total number of leukocytes and on the differential proportion.

The determination of dosage.

The effect of the drug on the splenectomized animal.

The effect on the erythropoietic function.

The effect on renal and hepatic function.

Pathologic changes after prolonged administration.

METHODS OF STUDY

Healthy full-grown mongrel dogs weighing between 4 and 12 kg. were used. An unlimited amount of dog biscuit, adequate for normal dogs, was their constant diet. The phenylhydrazine was given subcutaneously in an aqueous solution or by stomach tube. Bromsulphalein and phenolsulphonephthalein were used in the estimation of hepatic and renal function, respectively. Blood was obtained directly by ear puncture for the enumeration of erythrocytes, leukocytes and the differential count; 200 cells were counted (in the future we expect to count 500 cells). Hydrochloride of phenylhydrazine was used, and the dosage was calculated from the body weight.

GENERAL EFFECTS

No untoward general symptoms were noted in the dogs given doses approximating those used clinically, during the experiments. Thrombosis of the superficial veins, a frequent complication in polycythemia vera, was not noted. Vomiting occurred in a few instances after the administration of the drug by stomach tube, but this was rare. Subcutaneous injections were attended by some discomfort. The dogs did not gain or lose weight excessively, and they appeared to be well throughout the experiments. Augmented toxicity was not observed when the drug was given subcutaneously. Early in these experiments we were convinced of the equivalent action of the drug when it was given subcutaneously and by mouth. Recently Long has demonstrated that intraperitoneal administra-

tion is effective. The total dosage given to three animals was comparatively enormous; the dose for one was 1.26 gm. for each kilogram of body weight and for the other two only a little less. This would be equivalent to 88 gm. for a man weighing 70 kg. and enough to treat the average case of polycythemia vera for from four to six years. That the animals were well after being given these large amounts is evidence of the lack of toxicity of the phenylhydrazine hydrochloride in therapeutic doses.

EXPERIMENT 1. THE EFFECT OF A LARGE AMOUNT OF PHENYLHYDRAZINE

Four animals were selected for the study of the comparative effects of various doses on the general condition and on the number of erythrocytes. All four dogs were given, by stomach tube, a total of 60 mg. of phenylhydrazine for each kilogram of body weight. The first dog was given the full amount in a single dose on the first day of the experiment, the second dog was given the full amount in two equal doses on the first and second days, the third dog was given the full amount in three equal doses on the first, second and third days, and the fourth dog the full amount in ten equal doses on each of the ten days of the experiment. (fig. 1.) The reduction in the number of erythrocytes was almost equal in the four dogs at the end of the experiment. In the first dog erythrocytes were markedly reduced between the first and third days after which the reduction was more gradual until the eighth day when there was a slight increase. In the second dog the erythrocytes were markedly reduced between the fourth and sixth days. Between the first and fourth days the reduction was more gradual and there was an increase after the sixth day. In the third dog the reduction was more gradual although it was marked between the sixth and seventh days and was followed by some regeneration between the seventh and tenth days. In the fourth dog there was a uniform reduction from the first to the tenth day. From this experiment it seems reasonable to conclude that a reduction dose of phenylhydrazine will cause approximately equal reduction in erythrocytes at the end of a ten-day period whether it is given in a single dose or in divided doses. The rate of reduction, however, is variable, being maximal in the animals given single doses and minimal in the animals given the greatest number of doses. The latter method of administration is most desirable because of the gradual effect but the former can be used without apparent harm. This information has been of value in clinical experience and we have been able to shorten the refractory period (between the time the drug is first administered and the appearance of evidence of reduction) by increasing the dosage the first two or three days of treatment.

EXPERIMENT 2. THE EFFECT ON THE ABSOLUTE NUMBER OF THE LEUKOCYTES

The leukocytes.—An increase in the number of leukocytes has been noted clinically by Owen, Brown and Giffin and by Altnow and Carey (5). Leo-

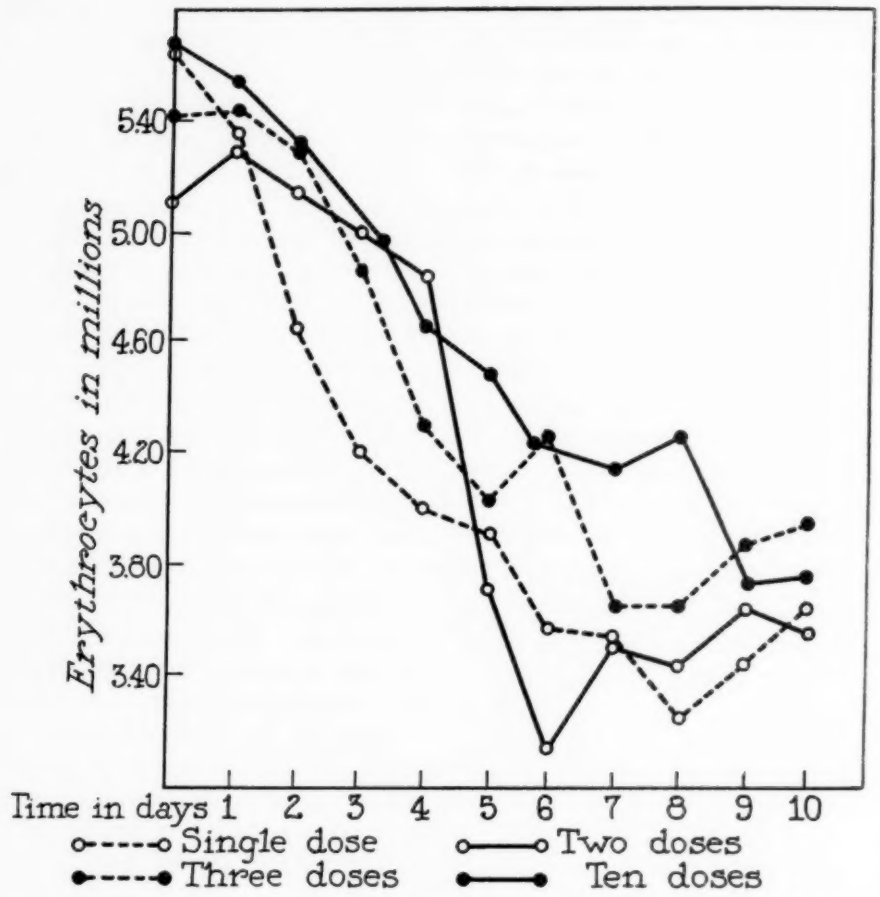
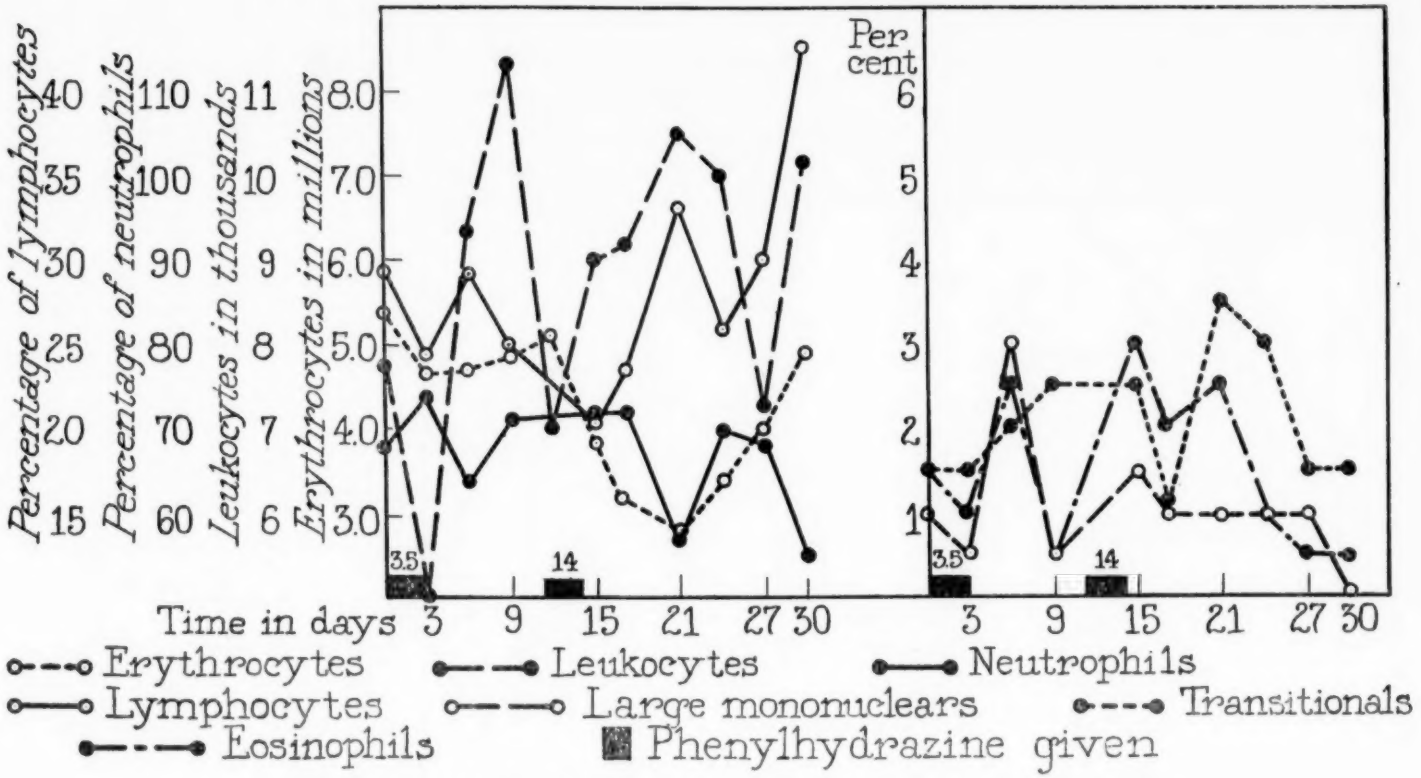


FIG. 1. The effect on the erythrocytes of 60 mg. of phenylhydrazine for each kilogram of body weight in single and divided doses.

pold (6) found no change clinically, and Long (7) could not demonstrate an increase in rabbits. Owen believed the number of leukocytes might indicate the rate of destruction of erythrocytes and that "the occurrence of a leukocytosis is a highly important index in controlling treatment." Our clinical experience has not supported this. Changes in the number of leukocytes in these experiments following the administration of phenylhydrazine were not constant. Thus there was an increase in the number of leukocytes following the administration of phenylhydrazine in ten experiments. (figs. 2, 3, 4, 5, 6 and 7, *d*, *e*, *f*, *g*, *h*, and no increase or a slight reduction in four experiments (figs. 7, *a*, *b*, *c*, and 8). Theoretically the factors which might influence this variation are the amount of the drug, the period over which it was given, the method of administration, and previous administration. The methods of administration and previous adminis-

FIG. 2. The effect of experimentally administered phenylhydrazine on the number of leukocytes and the differential count. (In this and the following figures the numeral on the block representing the time of the administration of phenylhydrazine indicates the milligrams of phenylhydrazine for each kilogram of body weight.)



FIGS. 3, 4, 5, and 6. The effect of experimentally administered phenylhydrazine on the number of leukocytes and the differential count.

Erythrocytes in millions
Leukocytes in thousands
Percentage of neutrophils
Percentage of lymphocytes
Per cent
Time in days
Erythrocytes
Neutrophils
Leukocytes
Lymphocytes
Large mononuclears
Transitionals
Eosinophils
Phenylhydrazine given

FIGURE 4

Percentage of lymphocytes
Percentage of neutrophils
Leukocytes in thousands
Erythrocytes in millions
Per cent
Time in days
30
Erythrocytes
Leukocytes
Large mononuclears
Neutrophils
Lymphocytes
Transitionals
Phenylhydrazine given
Eosinophils

FIGURE 5

FIGURE 5

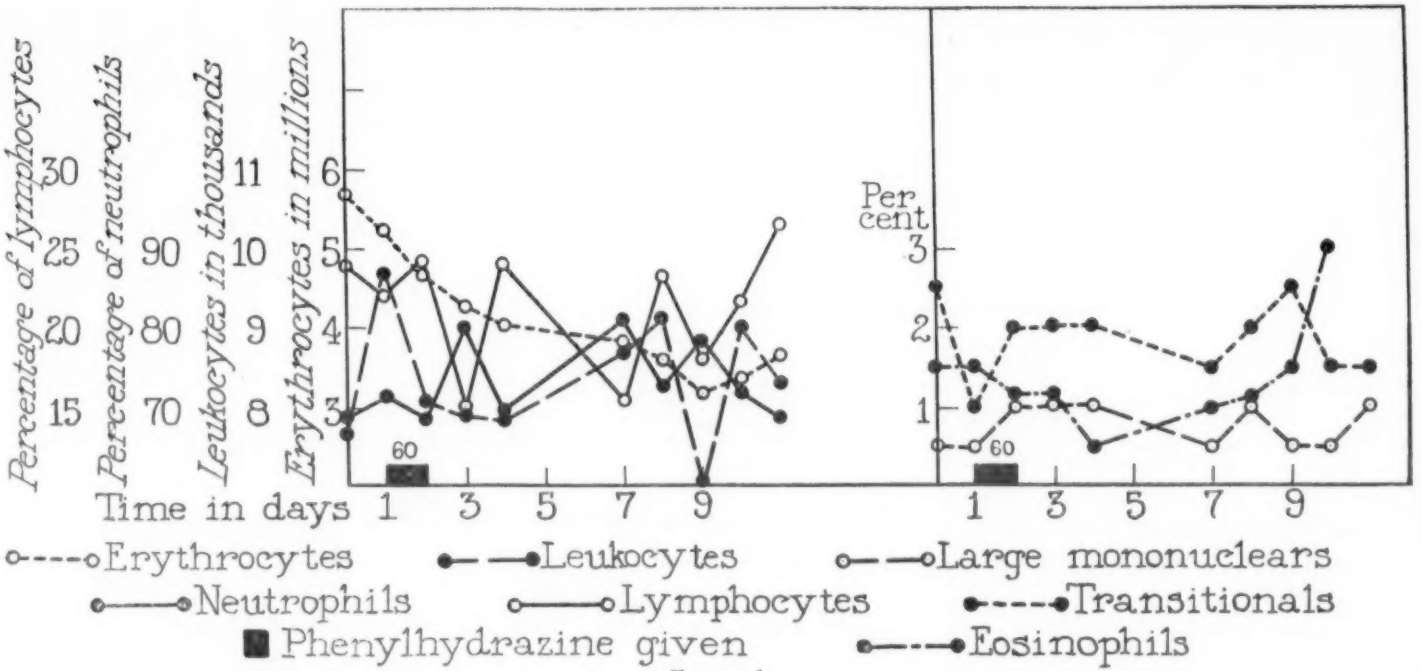


FIGURE 6

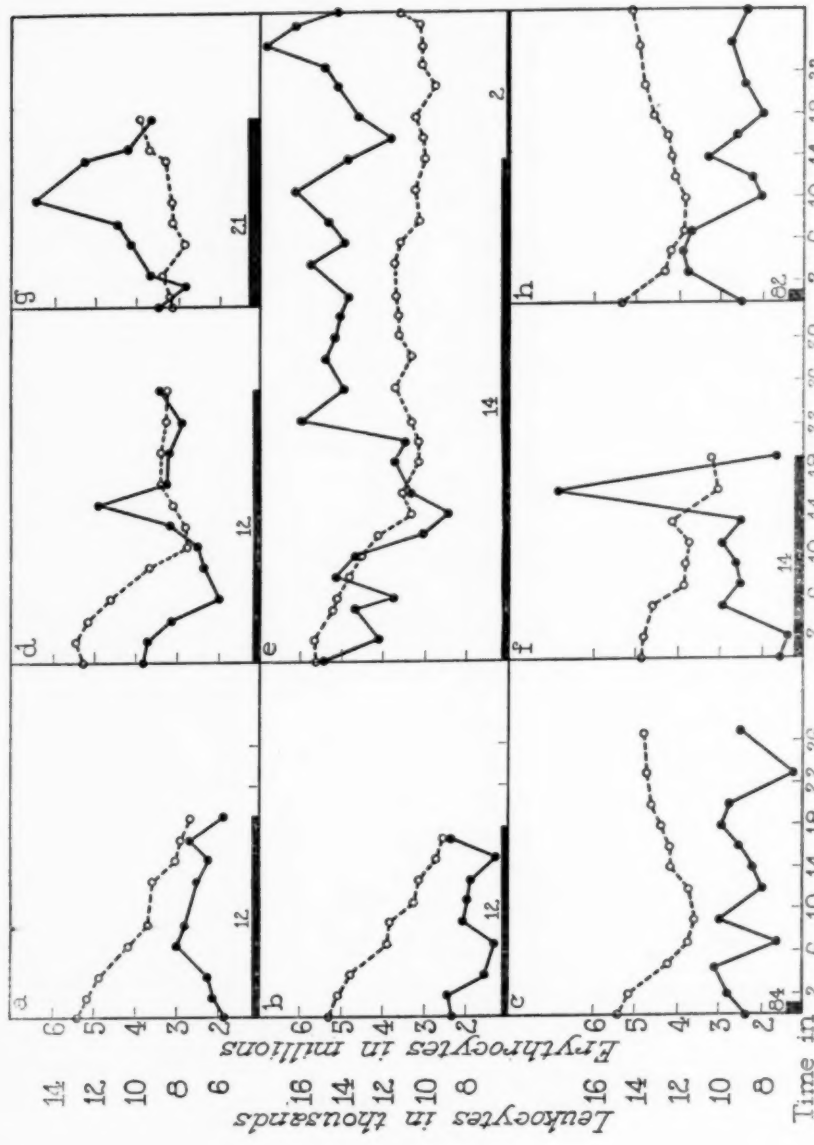


FIG. 7. The result of experimentally administered phenylhydrazine on the number of erythrocytes and leukocytes. The results of eight separate experiments are shown.

FIG. 8. The effect of experimentally administered phenylhydrazine on the number of leukocytes and the differential count.

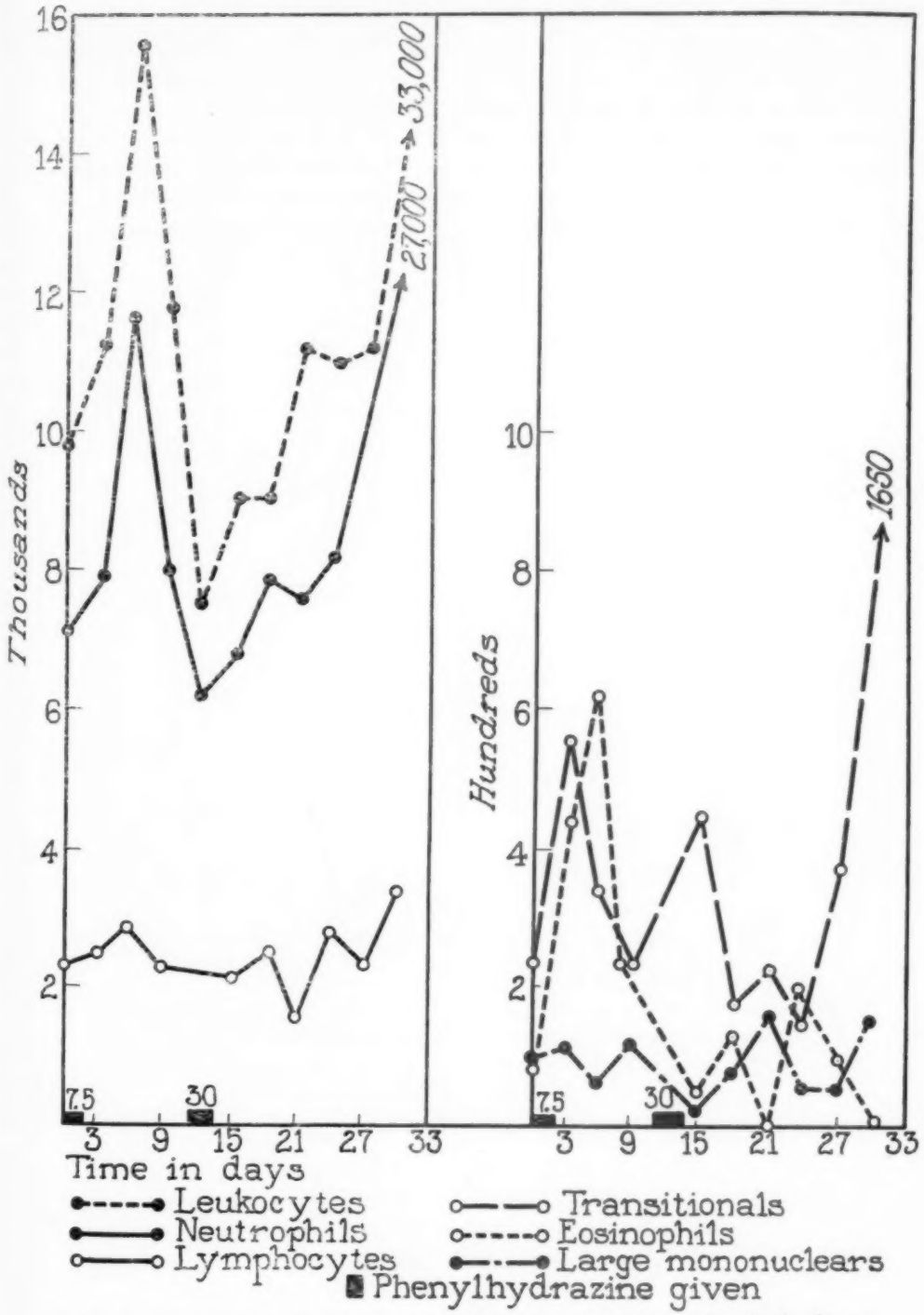
tration apparently were not factors. The most frequent and the most marked increases in the number of leukocytes were found in animals given rather large amounts of the drug on one or two days. The outstanding exception is shown in figure 7*c*; there was very little response after the administration of 48 mg. of phenylhydrazine for each kilogram of body weight. Appreciable increases were noted in two animals (fig. 7 *e*, *g*,) which were given phenylhydrazine daily.

The cause of the leukocytosis has been debated. Owen's work led him to believe that the leukocytosis was secondary, and probably the result of tissue destruction rather than stimulation of the bone marrow. Brown and Giffin believe that their clinical experience indicates that the drug exerts specific stimulation on the production of leukocytes, and Altnow and Carey conclude that there is a direct stimulating effect on the bone marrow. The results in our experiments were variable. In three instances (figs. 2, 3, and 4) there was apparently a specific response, which was independent of the effect on the erythrocytes, as the number of leukocytes increased soon after the drug was given and returned to a lower level after withdrawal of the drug at a time when the number of erythrocytes was decreasing rapidly. However, in four experiments (figs. 6 and 7 *d*, *f*, and *h*) the leukocytosis could well have occurred secondarily.

Our data, therefore, indicate an irregular response of the leukocytes with an increase in most instances which was at least frequently due to the specific action of phenylhydrazine and was not a result of the destruction of erythrocytes or other tissues. Two factors might contribute to this irregularity of response: prolonged action of phenylhydrazine after withdrawal which indicates either storage or slow excretion, and destruction of erythrocytes which continues even when the number of erythrocytes in the peripheral blood is increasing. A consideration of these factors makes it impractical to conclude that the secondary effects of the drug are responsible for the leukocytosis, and it also modifies the assumption of a specific stimulating effect of the drug on the production of leukocytes, for proof is lacking of the absence of increased destruction of erythrocytes when the number is stationary or increasing. Instances in which the leukocytosis decreases or disappears immediately following the discontinuance of phenylhydrazine offer evidence of a specific stimulating action.

The neutrophils.—The results of four experiments (figs. 9, 10, 11 and 12) during which the number of leukocytes was markedly increased, were used for the calculation of the absolute number of neutrophils, lymphocytes, eosinophils, transitionals and mononuclear cells. In each of these experiments there was almost an exact parallelism between the total number of leukocytes and the total number of neutrophils.

The lymphocytes.—The lymphocytes showed a somewhat more variable response than the neutrophils. In four instances there was, however, a rough



FIGS. 9, 10, 11, and 12. The effect of experimentally administered phenylhydrazine on the absolute number of leukocytes.

parallelism between the absolute number of leukocytes and lymphocytes, an increase or decrease in one being associated with the same change in the other (figs. 9, 10, and 11, second administration, and fig. 12, after the seventh day). In figure 11 there was a decrease of lymphocytes (third day) followed by an increase which was associated with an increase of leukocytes. In two experiments (figs. 9, and 11, first administration) there was very little change in the total number of lymphocytes associated with definite increases in leukocytes.

The transitionals.—The absolute number of transitional cells ran nearly parallel to the absolute number of leukocytes and was almost always well above normal. In one instance the remarkable number of 1650 transitionals was found; this, however, was only on one day.

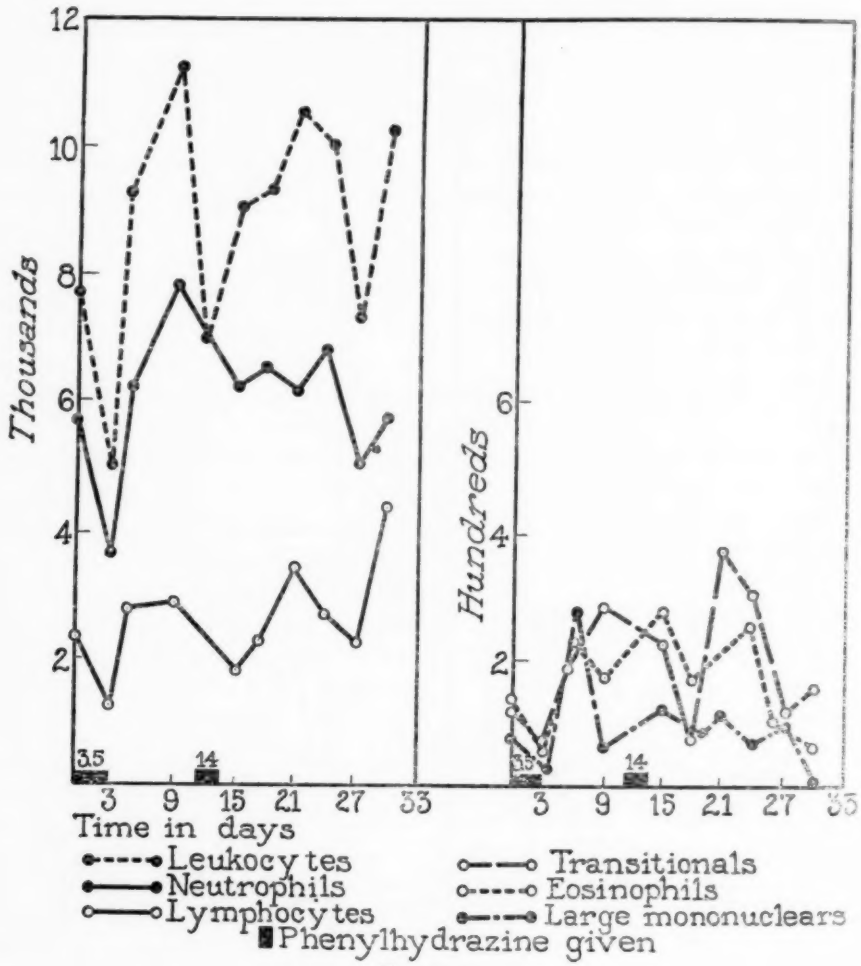


FIGURE 10

The eosinophils. — The absolute number of eosinophils was variable. An increase in the number of leukocytes was associated with a similar change in the absolute number of eosinophils in three instances (fig. 9, fifth day, and fig. 10, ninth and twenty-first days), a decrease in two instances (fig. 12 seventh day and fig. 10, thirtieth day) and no change in two instances (fig. 9 twenty-seventh day, and fig. 11). A decrease in the number of leukocytes was associated with an increase in the number of eosinophils in one instance (fig. 12, tenth day).

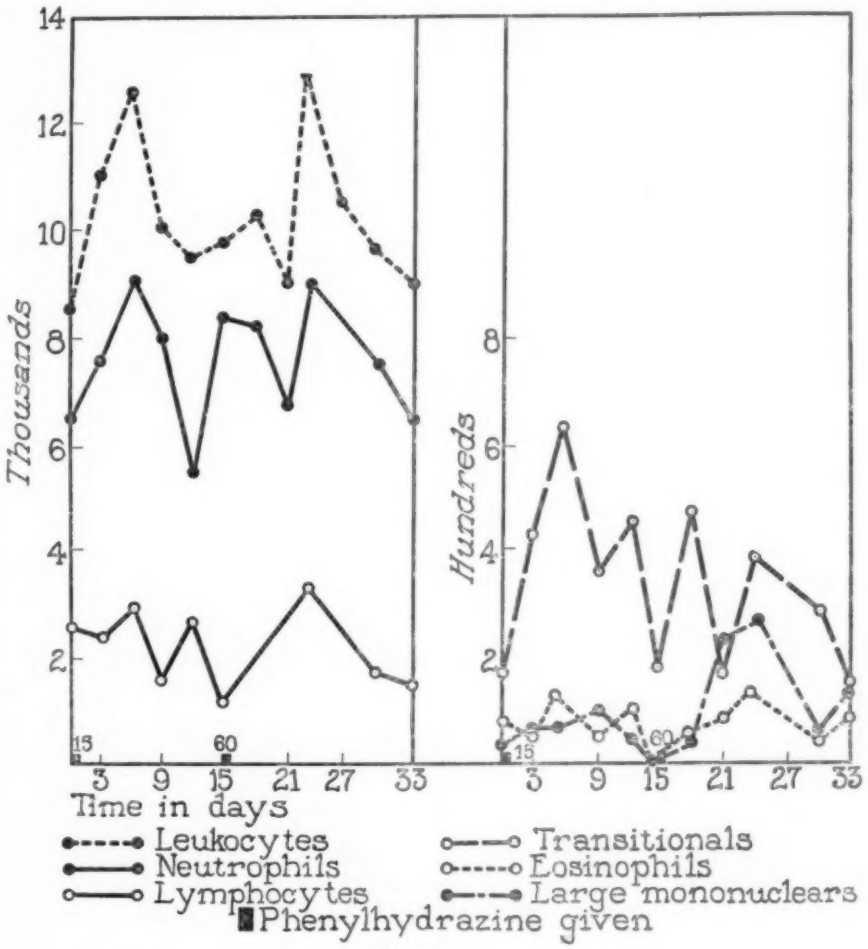


FIGURE 11

The mononuclears.—Increases in the number of leukocytes were associated with a definite increase in the total number of large mononuclear cells in three instances (fig. 9, twenty-first day, fig. 11, twenty-fourth day, and fig. 12, fourth day), but with a decrease in one instance (fig.

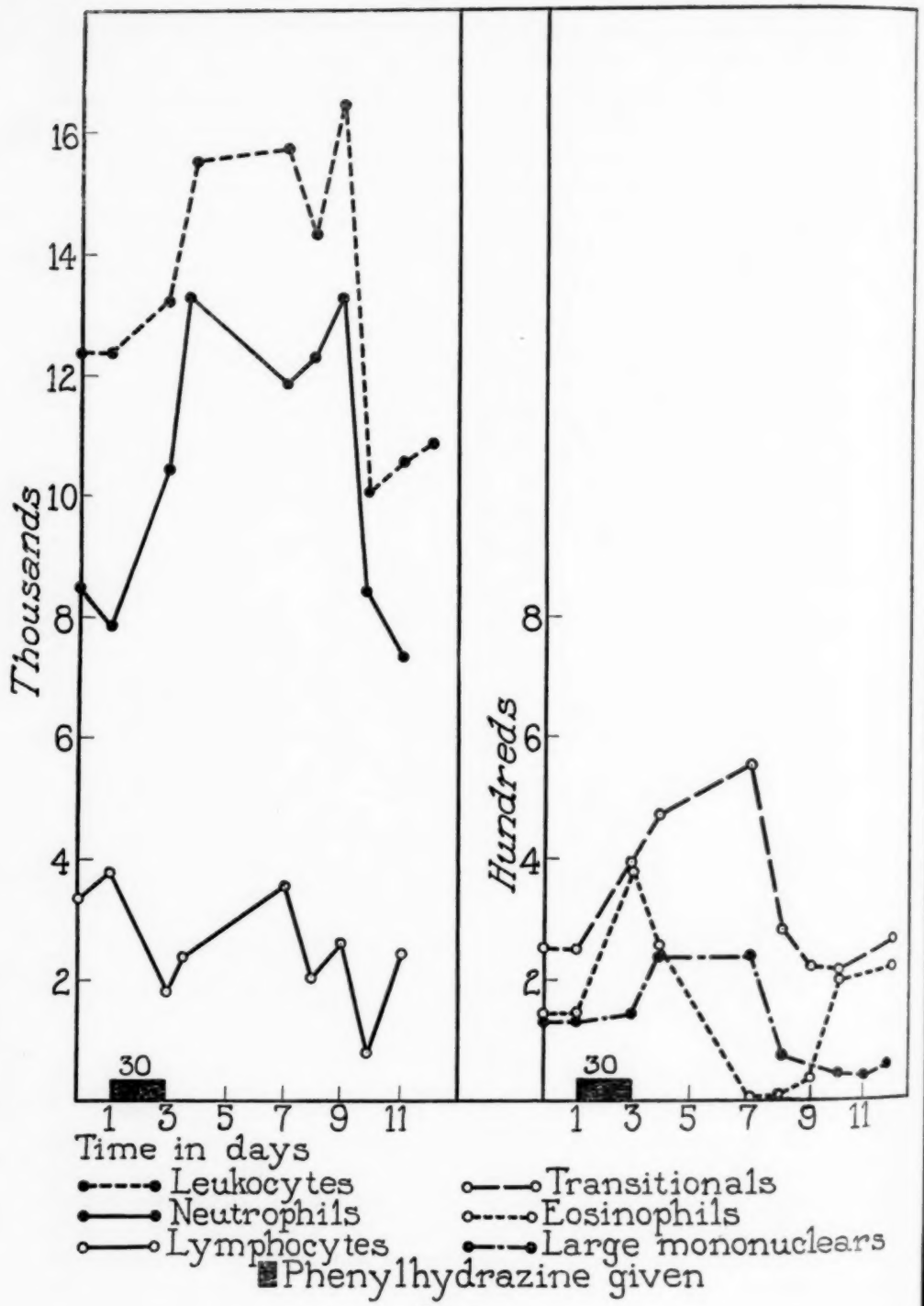

Thousands
16
14
12
10
8
6
4
2
Hundreds
8
6
4
2
30
30
1 3 5 7 9 11
1 3 5 7 9 11
Time in days
Leukocytes
Neutrophils
Lymphocytes
Transitionals
Eosinophils
Large mononuclears
Phenylhydrazine given

FIGURE 12

9, twenty-seventh day) and very little change in four instances (figs. 9 and 11, sixth day, fig. 10, ninth and twenty-first day). All of these changes were very small.

Comment on Experiment 2.—These data indicate a somewhat irregular response in the absolute number of neutrophils, lymphocytes, eosinophils, transitionals and mononuclears with, in most instances, parallel changes in the numbers of these cells when compared with changes in the total number of leukocytes. The neutrophils and transitionals showed the greatest increases.

Experiment 3. The effect on the differential percentage of leukocytes

The neutrophils.—In four experiments (figs. 2, second administration, 4, 5, and 6) there was an increase in the percentage of neutrophils. In all of these cases there had been an increase in the total number of leukocytes. The increase in the percentage of neutrophils in each of these cases was roughly in proportion to the decrease in the percentage of lymphocytes. In one animal (fig. 3) there was a decrease in percentage of neutrophils associated with an increase in the total number of leukocytes. In two instances (figs. 2, first administration, and 8) there was no definite change in the percentage of neutrophils. In the first instance there was an increase in the total number of leukocytes and in the latter there was no increase. Although these data represent variable effects there is evidently a tendency to a relative increase of the percentage of neutrophils, porportionate to a decrease in the lymphocytes.

The lymphocytes.—The change in the percentage of lymphocytes was extremely variable. There was definite increase in five animals (figs. 2, first administration, 3, second administration, 4, second administration, 6 and 8) but a decrease in the percentage of lymphocytes in four animals (figs. 2, second administration, 3, first administration, 4, first administration, and 5). Comparison of these changes with the changes in the percentage of neutrophils shows roughly a shifting mechanism between these two components, that is, a relative increase in neutrophils with a decrease in the lymphocytes, or vice versa.

The transitionals.—There was a definite increase in the percentage of transitional cells in all animals. (figs. 2, 3, 4, and 8) with one exception (fig. 6) in which there was little change. This increase was marked, in some cases increasing rapidly from a normal of 2 per cent to a high level of 5 per cent.

The mononuclears.—There was no change in the percentage of mononuclear cells (figs. 2, 4, 5, 6, and 8) with one exception (fig. 3) in which there was an increase.

The eosinophils.—Changes in the proportion of eosinophils were neither constant nor great. There was, however, a definite increase in several experiments (figs. 2, 4, 5, 6, and 8). In the experiment illustrated in figure 6 the increase occurred several days after phenylhydrazine had been discontinued and was probably not due

to the drug. In one instance (fig. 2, second administration) there was no significant change.

The basophils.—Basophilic cells are normally so few in the blood of dogs that there may be none in 200 leukocytes. These cells were carefully observed in the experiments, but no significant change was found.

Comment on Experiment 3.—These data on changes in the percentage of neutrophils, lymphocytes, eosinophils, mononuclears and transitionals indicate an irregular response. The most common observations were an increase in the percentage of neutrophils with a decrease in the percentage of lymphocytes; occasionally the reverse was true, increase in the percentage of transitional cells, slight change in mononuclears, and little change, usually slight increase, in the percentage of eosinophils.

Owen noted relative polymorphonuclear leukocytosis in a case of polycythemia vera treated with phenylhydrazine. Altnow and Carey studied one case in greater detail. They found that the absolute number of polymorphonuclear eosinophils and neutrophils increased and the number of lymphocytes and mononuclear cells did not change or were diminished. Hence they concluded that phenylhydrazine stimulated the bone marrow, but failed to stimulate or actually depressed the reticulo-endothelial system. These authors mention the incompleteness of their data as studies were not begun until the thirteenth day after treatment was begun and three days after the drug had been discontinued. Benzol and radium treatment had been given previously.

Our data are in accord with those of Altnow and Carey with respect to the usual increase of polymorphonuclear neutrophils and eosinophils but this increase did not always occur. In contrast to their data, however, the absolute number of lymphocytic, mononuclear and transitional cells frequently increased in our experiments. We did not find the increase in basophils noted by them. We could not detect stimulation of the production of any type of cell to the absolute exclusion of others.

Experiment 4. The effect of dosage

Reduction dose.—A reduction dose of phenylhydrazine is one which will cause definite and progressive diminution in the number of erythrocytes. The reduction of erythrocytes in response to a given amount of phenylhydrazine is fairly uniform, provided the period over which it is given is not too prolonged. This is shown (fig. 13) in the first two instances in which phenylhydrazine was given to cause a decrease in the number of erythrocytes in the three animals. In the first administration (fig. 13) Dog *a* received (over a period of three days beginning November 16, and three days beginning November 27) a total of 52 mg. for each kilogram of body weight, Dog *b* received (over a period of two days beginning November 16 and two days beginning November 28) 75 mg., and Dog *c* received (November 16 and November 29) 75 mg. The amount of destruction was almost equal in all cases. In the second administration (beginning December 25) each dog received 60 mg. for each kilogram of body weight with approximately equal

FIG. 13. The effect of experimentally administered phenylhydrazine on the number of erythrocytes. The references in the text to "first administration," "second administration," and "third administration" refer respectively to the inclusive dates November 16 to 30, December 24 to March 9, and April 6 to June 22. The effects on three animals are shown.

decreases in the number of erythrocytes. This uniform response to a certain amount of the drug is also demonstrated in all three animals in the third administration (fig. 13, April 6) as a result of 12 mg. for each kilogram of body weight, given daily. In calculating the decrease in erythrocytes for each milligram of phenylhydrazine for each kilogram of body weight, the amount of the drug given at each dose must be considered. Thus in the three animals (fig. 13, first administration) to which phenylhydrazine was administed over a period of one to three days the average dosage was 67 mg. for each kilogram, the average decrease in erythrocytes was 2,550,000 and the average decrease in erythrocytes for each milligram of phenylhydrazine for each kilogram of body weight was approximately 38,000 (2,550,000 ÷ 67). Beginning April 6, smaller doses, given daily with an average dosage of 268 mg. for each kilogram of body weight, produced an average reduction in number of erythrocytes of 2,330,000, or roughly 9,000 for each milligram of phenylhydrazine for each kilogram of body weight. The latter method of administration more nearly parallels that used clinically. In the cases reported by Brown and Giffin the average weight was 65 kg., the average dose was 5.2 gm. and the average reduction of erythrocytes was 3,800,000. Calculated on this basis each milligram of phenylhydrazine for each kilogram of body weight caused a reduction of 47,500 erythrocytes for each millimeter. This number is high compared to that obtained in experimental animals, and the difference is probably explained by the greater susceptibility of the erythrocytes in polycythemia vera.

Maintenance dose.—A maintenance dose of phenylhydrazine is one which will keep the number of erythrocytes at a more or less constant low level. It is apparent from many experiments that a reduction dose of phenylhydrazine within certain extremes, if given daily over a long period, becomes a maintenance dose and there is no further reduction in the number of erythrocytes. Examples of this are shown in figure 7 *d, e, f* and in figure 13 (Dog *a*). In the first instance 12 mg. for each kilogram of body weight was given daily and the reduction of erythrocytes was more than 2,000,000. On the eleventh day there was no further change and between the eleventh and twenty-sixth days there was a slight increase in erythrocytes. In the experiment illustrated in figure 7 *e*, 14 mg. for each kilogram of body weight was given for sixty-two days. There was active reduction of the number of erythrocytes until the fourteenth day, after which no change occurred. In the experiment illustrated in figure 7 *f* there was no change after the sixteenth day although phenylhydrazine was given daily. In figure 7 *a*, 12 mg. proved to be an active reduction dose, although given over a long period of time (fig. 13, Dog *a*) it did not cause the number of erythrocytes to go below 3,000,000.

There is a wide variability in the maintenance dose of phenylhydrazine. In two animals it was 14 mg. for each kilogram of body weight (fig. 7, *e. f*) while in one it was 12 mg. (fig. 13, Dog *a*, January 9); later (April 27) in the two animals (fig. 13, Dogs *b*

and *c*) 6 mg. for each kilogram of body weight was adequate. In the experiment illustrated in figure 7 *e*, 2 mg. was inadequate to keep the number of erythrocytes at a low level. Since it has been shown (in the description of reduction dosage) that phenylhydrazine has a direct quantitative action, the explanation of this variation probably lies in the fact that after a certain degree of anemia is obtained there is a compensating mechanism which causes new cells to be thrown into the circulation more rapidly. Thus, although 14 mg. for each kilogram of body weight given daily is a maintenance dose it is not a minimal maintenance dose; the minimal maintenance dose in dogs may be 6 mg. or less. Even this small amount is much greater than that which clinical experience has shown to be warranted in the treatment of patients with polycythemia vera. In fact this minimal maintenance dose in dogs is an adequate reduction dose in man. The explanation of this is not clear, but it is probably due to a greater susceptibility of the erythrocytes in polycythemia vera.

Summary

Dogs given phenylhydrazine hydrochloride for 146 days in a period of eight months and a total dosage comparable to that of from four to six years of treatment of polycythemia vera in man, were well at the end of the experiments.

The drug had equal effects whether given subcutaneously or by stomach tube.

The same doses of phenylhydrazine produce approximately equal erythroclastic effects whether given in a single dose or in divided doses within a ten-day period.

Although the response is irregular there is a tendency toward an increase in the number of leukocytes, which in some instances is apparently due to specific action of the drug, and not to tissue destruction.

Although there was an irregular response in the absolute number of neutrophils, lymphocytes, eosinophils, transitionals and mononuclears there was in most instances a rough parallelism between changes in the numbers of these cells, and in the total leukocytes.

The transitional cells uniformly increased in percentage. The neutrophils increased in some instances and decreased in others. The percentage of lymphocytes varied in inverse proportion to the percentage of neutrophils. There was little change in the percentage of the mononuclear cells and eosinophils: in the latter there was a slight tendency toward increase. Basophils were so infrequently seen that they have been disregarded in this report.

Each milligram of phenylhydrazine for each kilogram of body weight caused a decrease of 38,000 erythrocytes when given in comparatively large doses within a three-day period, and as little as 9,000 when given over long periods in smaller doses. Clinically, in polycythemia vera a decrease of 47,500 cells has been demonstrated, a difference which is probably due to increased susceptibility of the red cells in polycythemia vera.

A reduction dose may become a maintenance dose if continued. The reason for this is not clear, but is prob-

ably explained by secondary stimulation of the bone marrow.

One must be exceedingly wary in drawing conclusions for clinical application from this experimental work. In the consideration of these data two facts must be borne in mind; the condition of the blood in normal dogs is not comparable to that in patients with polycythemia vera, and the reaction of these animals to phenylhydrazine may be different as a result of the difference in species. We have, however, attempted to duplicate as nearly as possible the clinical administration of phenylhydrazine.

Experiments With Phenylhydrazine†

II. Studies On Renal and Hepatic Function and Erythropoiesis*

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and
HERBERT Z. GIFFIN, M.D., *Division of Medicine, Mayo Clinic, Rochester, Minnesota*

LEVI (8) first remarked on the danger of inducing permanent changes in the liver by treating cases of polycythemia vera with phenylhydrazine. He reported a case in which 7.5 gm. of phenylhydrazine hydrate had been administered in eighteen months. Death occurred from erysipelas. Necropsy showed cirrhosis of the liver, but Levi did not consider the drug necessarily causal, as cirrhosis of the liver is often noted in cases of polycythemia vera untreated with phenylhydrazine. Studies of the function of the liver following the administration of phenylhydrazine have not been numerous. Brown and Giffin (1296) (3) were unable to demonstrate dye retention in patients after single courses of treatment with a total dosage of from 3 to 6 gm. of the drug. Several of their cases which have been studied since that report, after three or four courses of treatment, do not show dye retention. Stealy's (9) patient has been treated for three years without manifesting gross evidence of hepatic injury, and functional studies showed no change. Leopold (6) noted absence of dye retention in one case after the administration of 2.0 gm. of the drug. Bodansky (10) gave 360 mg. divided into four doses to a dog weighing 5.9 kg. Studies on the carbohydrate tolerance gave evidence of marked hepatic injury. This dosage would be equivalent to 1 gm. of phenylhydrazine each day for four days for a man weighing 70 kg., a much larger dose than that which is used therapeutically. Moreover, there is no evidence that the injury was more than temporary. Long (7) gave rabbits weighing 2 kg. 3 mg. intraperitoneally in a single dose and found a slight lag in the excretion of tetrachlorphenolphthalein.

Studies of renal function in experiments with phenylhydrazine are much more infrequent than those on the liver. Brown and Giffin reported no change after single courses. Since then some of their cases in which repeated courses were given have shown no evidence of reduction in renal function. In Stealy's case treated

*The material in this paper was presented in a thesis by Edgar V. Allen to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M. S. in Medicine, 1928.

with phenylhydrazine for three years blood urea and excretion of phenolsulphonephthalein were normal.

Experiment 1. The effect of phenylhydrazine on renal and hepatic function

Three dogs were each given 146 daily doses of phenylhydrazine in a period of eight months (fig. 13 Study I). The function of the kidneys was studied by means of the phenolsulphonephthalein test, blood urea and urinalysis. The hepatic function was studied by the dye excretion method and the data are shown in the tabulation. The final readings in each instance were taken one month after phenlyhdrazine had been discontinued. A survey of the tests shows that during the nine month period there was an average diminution of 27 per cent in the phenolsulphonephthalein excretion by the kidneys. Urinalyses showed no change. Whether this diminution in phenolsulphonephthalein excretion is significant cannot be predicated. The final readings of the phenolsulphonephthalein excretion in each instance were within normal limits. The absence of abnormal urinary conditions would indicate absence of acute processes in the kidney and the absence of marked organic lesion. In some instances, while phenylhydrazine was being administered, the blood urea was slightly increased, but not permanently. This has also been shown clinically by Huffman, (1) and Brown and Giffin. The former believed this was largely due to "renal flooding." These data indicate that the excretive function of the kidneys for nitrogenous products is adequate, but it is possible that the margin of safety has been encroached on. Studies of hepatic function by the dye excretion method showed only slight retention of dye in one of three animals (Dog *b*, tabulation). Dogs *b* and *c* (tabulation) were killed and necropsy was performed. The pathologic aspects will be discussed in Study III.

Experiment 2. The effect on erythropoiesis

The rate of regeneration of erythrocytes was studied after various lengths of time in order to determine the effect of the drug on the erythropoietic function of the body. The results are shown in figure 13 Study I and figures 1 and 2. Fig. 13 shows the rate of increase in the number of erythrocytes beginning at the end of the third week following six daily doses, at the end of the fourteenth week following seventy daily doses, and at the end of the thirty-second week following 146 daily doses. Figures 14 and 15 show the results in dogs *a* and *c* illustrated on a larger scale. The three curves show but little variation and indicate that regeneration occurs as rapidly after prolonged phenylhydrazine administration as it does after a very short course. The number of erythrocytes did not remain at a new and lower level after prolonged phenylhydrazine administration, and there was no indication that the erythropoietic function of the body was depressed.

In all three animals a peculiar cycle of anemia occurred after the complete withdrawal of the drug (fig. 13, June

TABLE I

THE EFFECT OF PROLONGED ADMINISTRATION OF PHENYLHYDRAZINE ON FUNCTION OF THE LIVER AND THE KIDNEYS

Dog	Date, 1927	Renal function		Hepatic function,	Specific gravity	Urine					Carbon dioxide combining power, volume, per cent	Blood chlorides, mg. per cent
						Graded 0 to 4						
		Phenolsulphonephthalein, per cent	Blood urea, mg. p.c.			Albumin	Casts	Erythrocytes	Leukocytes	Sugar		
a	1-27		60								48	610
	2-23	75	30								44	689
	4-13		27	0								
	4-20	75	36		1.032	1	0	1-	1	1-		
	7-5	50	42	0	1.033	1	0	1-	2	0		
	7-28	40	34	0	1.031	1	0	0	1	0		
b	1-27		20									660
	2-23	75	23								58	680
	4-6		27									
	4-20		27									
	7-5	20-45	23	0	1.030	3	0	1-	1	1		
	7-28	60	16	1	1.007	1	0	0	0	0		
c	2-21		25								52	700
	2-23	90	15								39	690
	4-13		17	0								
	4-20	90	16		1.010	1	0	0	0	0		
	7-5	50	18	0	1.011	1		1-	1-			
	7-28	60	10	0	1.012	1	0	0	0	0		

22). The return to normal was similar to that which, from clinical and previous experimental study, one would expect. After a period, during which the number of erythrocytes was normal, anemia occurred in much the same manner as if phenylhydrazine had been given. After a prolonged period of anemia the count rose again to normal more slowly than is usual following phenylhydrazine administration.

EXPERIMENT 3. THE EFFECT OF SPLENECTOMY

Splenectomy had no effect on the action of phenylhydrazine on the erythrocytes in two dogs. This fact eliminates the spleen as the site of action.

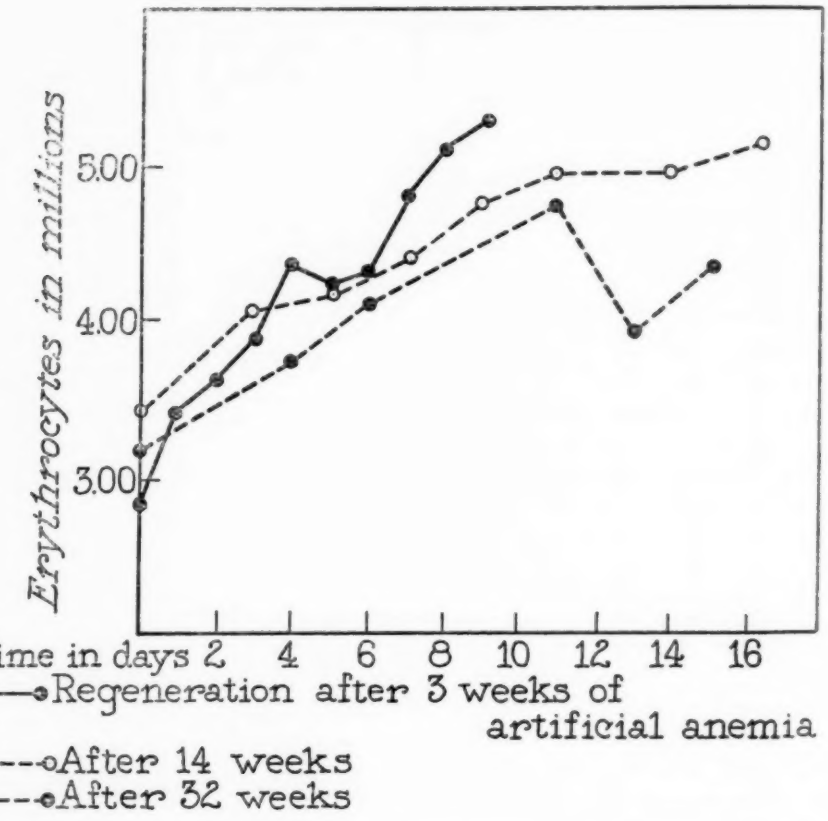
Long has previously reported a similar result in rabbits.

Summary

Each of three dogs was given a total dosage of approximately 1.26 gm. of phenylhydrazine hydrochloride over a period of eight months, the equivalent of from four to six years of clinical treatment in man. The final studies of renal and hepatic function were made one month after the drug had been discontinued.

There was an average reduction of 27 per cent in phenolsulphonephthalein excretion, but the final readings were within normal limits. Urinalyses were negative; blood urea estimations were normal. These data indicate that the renal function was adequate after prolonged treatment, but they do not prove that the kidneys were not impaired by the drug.

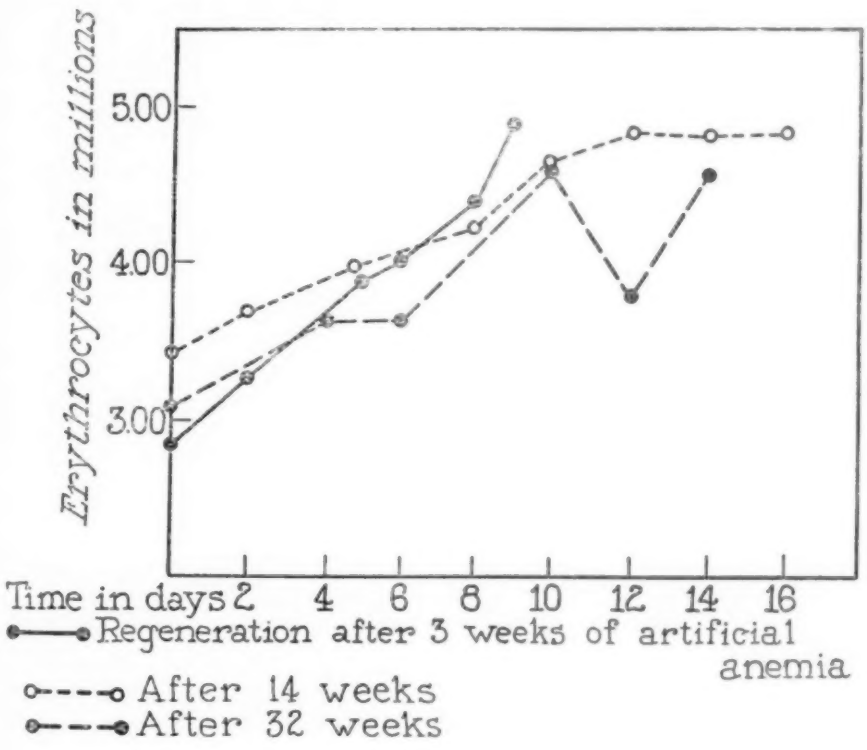
Only one of three dogs receiving similar amounts of phenylhydrazine showed reduction in dye excretion



Figs. 1 and 2. Rate of regeneration of erythrocytes after treatment with phenylhydrazine.

from the liver. This change was small and of questionable significance. The rate of regeneration of erythrocytes was unchanged.

The removal of the spleen was without influence on the effect of phenylhydrazine on the number of erythrocytes.



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Experiments With Phenylhydrazine

III. Pathologic Anatomy*

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IN Studies I and II methods were suggested which were believed essential for a comprehensive survey of the effects of phenylhydrazine. In brief these are: the effect on the blood, the effect on the function of the liver and kidneys, the effect on erythropoiesis, and the pathologic changes induced by prolonged administration of phenylhydrazine in doses sufficient to affect the erythrocytes which is comparable to that produced clinically. Criticism of conclusions drawn from previous work was that they were not based on results following experimental dosage comparable to that used clinically, and that results following the use of compounds allied to phenylhydrazine were too often regarded as produced by phenylhydrazine itself. The preceding studies included experiments on the blood, on the function of the liver and kidneys and on erythropoiesis. This report is on the results of a study on the pathologic anatomy.

Records in the literature with regard to the effect of phenylhydrazine on the structure of organs have not been numerous. Underhill (1) gave 50 mg. of phenylhydrazine to a dog weighing 10 kg. Since he was interested primarily in the effect on the blood sugar, he did not report the effect on the erythrocytes nor the time of necropsy. At necropsy all organs appeared normal except the liver and spleen, the former of which was of a peculiar chocolate-brown color. The spleen was enormously enlarged and dark. Microscopic studies were not reported. It seems probable to us that the changes in the liver and spleen were temporary and due to destruction of erythrocytes. Levi (2) reported the necropsy data in a case of polycythemia vera treated with phenylhydrazine. The patient was a man aged fifty years who had received 7.5 gm. of phenylhydrazine in a year and a half and died following erysipelas. At necropsy the spleen was enlarged, was rich in leukocytes and contained excessive blood pig-

*Submitted for publication February 9, 1928.

The material in this paper was presented in a thesis by Edgar V. Allen to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Medicine, 1928.

ment. The liver was of medium size with a slightly irregular surface and on section was of a peculiar yellowish color. Histologic study showed marked increase in the interlobular connective tissue which contained many round cells. Centers of regeneration were present. He believed that phenylhydrazine did not cause the cirrhosis but that this was due primarily to increased destruction of blood since it occurred in untreated cases; the phenylhydrazine may have exaggerated the normal course of events by increasing the destruction of blood. According to Owen (3), "whether repeated small doses of phenylhydrazine such as were given to patients will or will not be deleterious to the liver cannot be said yet." Bodansky (4) gave a dog weighing 5.9 kg. subcutaneous injections on four subsequent days, a total dose of 360 mg. of phenylhydrazine hydrochloride. Rapid reduction in the number of erythrocytes occurred and the animal was killed on the twentieth day. The spleen was greatly enlarged and microscopically showed hyperplasia and hematogenous pigmentation. Fatty changes were present in the cortical portion of the kidneys. The liver showed extensive "degenerative and necrotic changes" and hematogenous pigmentation. It seems essential to point out that the dosage in this experiment is the equivalent of 1 gm. of phenylhydrazine given daily for four days to a man weighing 70 kg. which is much more than a therapeutic dose. Long (5) gave rabbits weighing 2 kg. each a single dose of 30 mg. intraperitoneally. He found no histologic change in the liver. The spleen, lymph nodes and bone marrow contained a markedly increased number of phagocytic cells containing intact erythrocytes and increased pigmentation.

Experiment 1

The dog used in this experiment was given 146 daily doses of phenylhydrazine hydrochloride by stomach tube in a period of eight months.* The amount was regulated to produce a moderate grade of anemia** and to simulate that used clinically in the treatment of polycythemia vera. The total dosage was 1.26 gm. for each kilogram of body weight, an amount sufficient in a case of polycythemia vera for from four to six years. Death was induced by the injection of air into the femoral vein twelve months after the beginning of the experiment and four months after phenylhydrazine had been discontinued. Complete necropsy was performed.

Gross examination.—The peritoneal and pleural cavities appeared normal. There was a slight amount of blood and air in the pericardial cavity. The epicardium, myocardium and heart valves did not show pathologic changes. The lungs appeared normal throughout. The spleen was of normal size. The cut surface was dark purplish brown with irregular still darker areas scattered throughout the substance. The liver was dark reddish brown. There were about ten scattered, discrete, grayish nodules just beneath the capsule measuring from 1 to 3 mm. in diameter. The cut surface appeared

*The functions of the liver and kidneys are reported in Study II, tabulation.

**Study I, figure 13.

normal and no other nodules were found. The gastro-intestinal tract, pancreas and adrenals did not show change. The kidneys were about equal in size. The capsules stripped easily leaving dark brown surfaces on which there were numerous irregular pits and scars, linear and roughly circular in shape. The cut surface showed that these scars were paler than the remainder of the renal parenchyma and were roughly pyramid shaped, their apexes extending well down through the cortex into the medulla, but not apparently to the pelvis (fig. 1). The kidneys otherwise appeared normal. The bladder and genitalia appeared normal.

FIG. 1. Depressions and connective tissue scars in the cortex and medulla of the kidney. The glomeruli are well preserved.

Microscopic examination.—Sections of the myocardium, lungs, spleen, pancreas, lymph nodes, and thyroid and axillary arteries stained with hematoxylin and eosin and the van Gieson stain did not show changes.

The kidneys appeared normal except for the scars already described. In the cortical portions of these the glomeruli were well preserved except that the tufts were slightly contracted and ischemic. In some, Bowman's capsule was slightly thickened. Very few tubules remained and these only as fragments. They were replaced by connective tissue consisting of a few lymphocytes and a larger number of endothelial and plasma cells with interspersed longitudinal bands and a scattered network of fibrous tissue. There were large areas of compact fibrous

tissue around some of the larger arteries near the corticomedullary juncture. In the medulla the scarred area consisted of a rather dense fibrous-tissue stroma in which were constricted collecting tubules. These scars were definitely delimited from the normal renal parenchyma (fig. 2). Sections specially stained showed no more fat than the kidney of a control dog. By special staining there was no iron (hemosiderin) except in the pyramidal scars which contained a rather large amount, most of it closely packed in large phagocytic cells.

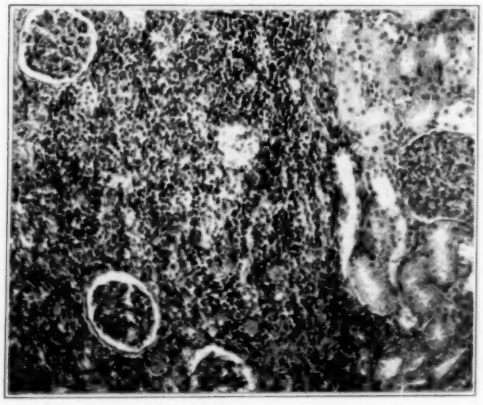

FIG. 2. Cortical portion of a cellular connective tissue scar in a kidney. The scar is definitely delimited and the glomeruli are well preserved.

The liver showed rather large pale parenchymal cells, close together, with a small amount of vacuolization which was present also in the liver of the control dog. There was rather marked capillary congestion. No fat was seen in the sections stained with scarlet red. A small grayish-white subcapsular nodule, one of those seen grossly, was found to be a collection of lymphocytes which extended from the capsule down to and around a portal space (fig. 3). A few other portal spaces were crowded with lymphocytes and in a few places these were found in the walls of the blood vessels. There were a few small collections of lymphocytes in capillary spaces, and a few around central veins. By special staining the amount of iron in the liver was found to be increased (grade 1), most of it phagocytosed and closely packed in large histiocytes and small amounts scattered diffusely in blood capillaries and in the connective tissue around the portal spaces. By special staining the amount of iron in the spleen also was shown to be increased (grade 1).

EXPERIMENT 2

This experiment was carried out in a manner comparable to the first experiment*. The animal was killed thir-

*Studies I and II, figure 13 and Tabulation.

teen months after the beginning of the experiment and five months after phenylhydrazine had been discontinued. Complete necropsy was performed.

Gross Examination. — The peritoneal cavity contained a few loose, easily broken, fibrous adhesions over the loops of small intestine, the omentum and the transverse colon. The pleural and pericardial cavities, and the lungs and heart appeared normal. The spleen was small and firm with numerous thickened, irregular, single and confluent, grayish-white areas in the capsule (hyaline perisplenitis). On the cut surface the trabeculae and malpighian corpuscles were distinct and close together. The liver was firm and deep purplish-brown with several darker brown areas measuring from 6 to 10 mm. in diameter on the surface. On the cut surface these extended just below the capsule. The substance of the liver was dark brown and homogeneous with indistinct markings. The stomach, intestines, pancreas and adrenals appeared normal. The left kidney had been removed one month previously. The pedicle remained as a clean healed amputation stump. The right kidney was normal in size. Its capsule stripped easily leaving a smooth brown surface on which there were a few scattered small pits. The cut surface appeared normal. The bladder was thick-walled, but its mucosa appeared normal. The genital organs appeared normal.

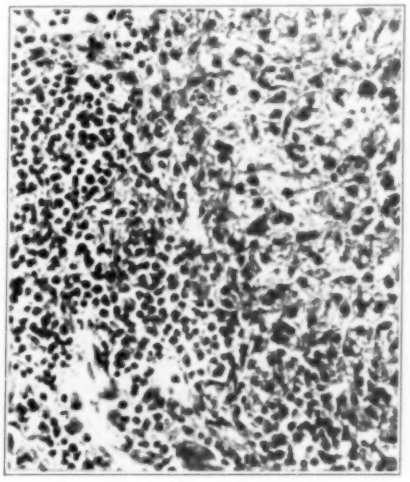

FIG. 3. A collection of lymphocytes beneath the capsule of the liver extending down to a portal space. The hepatic cells are normal.

Microscopic examination.—Sections of the lungs, pancreas, adrenals, iliac arteries, aorta, pectoralis major muscle and aortic lymph nodes, stained with hematoxylin and eosin and the van Gieson stain did not show anything

abnormal. The capsule of the spleen was irregularly thickened and composed of dense fibrohyalinized tissue with a few cell nuclei. The iron was increased (grade 1). The trabeculae were more numerous and closer together than normal. The liver showed rather large pale cells, crowded close together. No fat could be demonstrated. The darker areas observed by gross examination proved to be irregular subcapsular hemorrhages extending a short distance into the substance of the liver. There were no collections of lymphocytes. There was increased iron (grade 2) closely packed in large cells and deposited irregularly in some of the blood capillaries and in the connective tissue around the portal spaces.

EXPERIMENT 3

The dog used in this experiment was given 80 mg. of phenylhydrazine hydrochloride for each kilogram of body weight daily by stomach tube. The dog was moribund on the fifth day when he was killed by injecting air into the jugular vein. Complete necrospy was performed immediately.

Gross examination.—The blood was brown and did not coagulate easily. The pleural and pericardial cavities appeared normal. There were numerous brown nodules from the size of a pin-point to 3 mm. in diameter, in the omentum and in the fat around the pedicle of the spleen (apparently hemorrhages); otherwise the peritoneal cavity was normal. The myocardium was brown and the lungs were a peculiar brownish-gray. The spleen was firm and approximately normal in size. Its capsule was slate-gray and normally wrinkled. The cut surface was black and the corpuscles and trabeculae could not be seen. The liver was dark greenish-brown with a few small black areas on the surface from 2 to 3 mm. in diameter. The cut surface was greenish-brown and the normal markings were not seen. The gallbladder was distended. The stomach, intestines, pancreas and adrenals were slightly browner than normal, otherwise there was no change. The kidneys were chocolate-brown and there were a few irregular darker areas on the surface. They appeared swollen and tense. The capsules stripped easily when cut and the edges everted. The cortical striae were distinct, particularly at the corticomedullary juncture where they were alternately dark brown and light tan. Several dark brown patches extended through the cortex and outer portion of the medulla. There were a few submucous hemorrhagic areas in the urinary bladder. The genital organs appeared normal.

The myocardium, lungs, pancreas, adrenals and pectoralis major muscle when stained with hematoxylin and eosin and by the van Gieson method did not show changes except that the capillaries were engorged with blood cells and blood pigment. The malpighian corpuscles of the spleen were few and small. There was a marked decrease in the number of leukocytes. The sinusoids were dilated and packed with yellowish-brown material which apparently was blood pigment and erythrocytes in many stages of disintegration. However, there was no

more iron than seen in the spleen of the control dog. This was scattered diffusely and was pale-staining. The hepatic cells were smaller than normal and rather granular and deeply stained. The capillary spaces between them were dilated and contained in many places a rather large amount of blood pigment and disintegrated erythrocytes, some in small compact groups and some scattered diffusely with small iron granules and there was iron in the debris in their lumina (fig. 5). Iron was seen occasionally in the glomerular spaces also, but there was none in the glomerular cells or in the distal convoluted, Henle's loops, or collecting tubular cells. In the spleen there was approximately a normal amount of iron but it was scattered diffusely and pale-staining. In the cells of Henle's loops there was

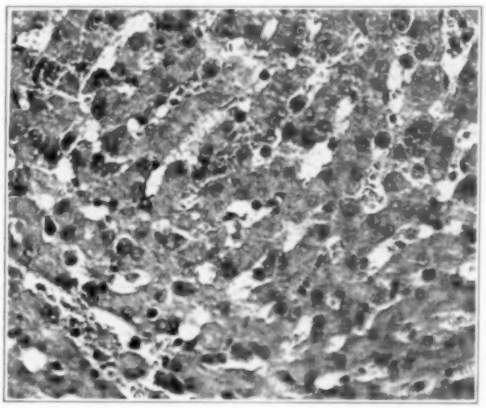

FIG. 4. Slight atrophy of the parenchymal cells of the liver and the dilated capillary spaces containing blood pigment and numerous phagocytic cells.

(fig. 4). No fat was seen. There was an abnormally large amount of rather pale-staining iron scattered diffusely throughout the capillary spaces, some of it apparently phagocytosed in large cells. The renal glomeruli appeared normal. The cells of the convoluted tubules were somewhat fragmented and irregularly stained, and appeared coarsely granular. There were several large irregular cystic spaces in the cortex, some of them containing small amounts of blood pigment. The cells of the proximal convoluted tubules throughout the cortex were packed considerably more than the normal amount of fat.

EXPERIMENT 4

This experiment was performed like the third experiment. The animal died on the fifth day. The body was placed at a temperature below freezing. Specimens from the liver and kidney were removed approximately sixteen hours after death. Complete necropsy was not performed.

Microscopic examination.—The hepatic cells, stained with hematoxylin

and eosin, appeared even more shrunken and deeply staining than those in the third experiment. The atrophy was particularly prominent around the central veins and portal spaces with corresponding dilatation of the capillary spaces. The latter contained scattered blood pigment and many phagocytes (fig. 6). However, iron could not be demonstrated. Sections stained with scarlet red did not show fat. The cells of the renal tubules were swollen and granular but fairly homogeneous (perhaps a postmortem change). In one section there were two rather large areas and numerous

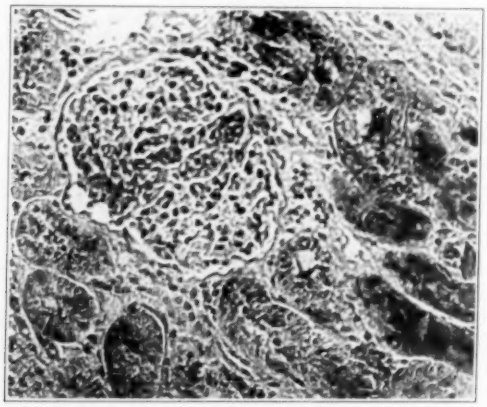

FIG. 5. Iron in a kidney, especially stained. The iron is the dark stained material in the lumina and cells of the convoluted tubules.

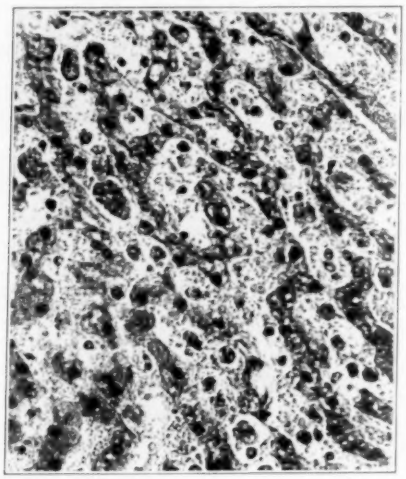

FIG. 6. Marked atrophy of the parenchymal cells of the liver, dilatation of the capillary spaces by blood pigment and numerous phagocytic cells.

smaller areas well beneath the surface which contained large numbers of plasma cells and endothelial cells closely packed together, crowded into and widely separating the interstices between the tubules and around the glomeruli. Near the centers of these collections of cells the tubules were constricted and atrophic (fig 7). There was no increase in fat. The same amount of iron was present in the proximal convoluted tubular cells and in the lumina of the tubules as in the third experiment except that it was more finely divided.

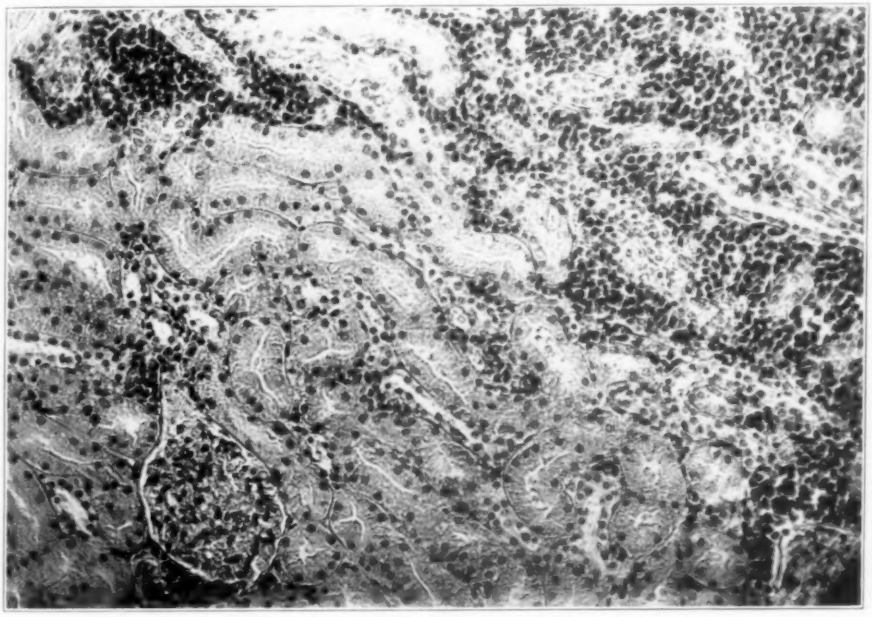

FIG. 7. Interstitial collections of plasma and endothelial cells in a kidney. The structure is otherwise normal.

EXPERIMENT 5

This experiment was similar to the fourth experiment. Specimens of the liver and kidneys were secured approximately sixteen hours after death. Complete necropsy was not performed.

Microscopic examination.—The cells of the liver were shrunken and deep-staining. The capillary spaces contained blood-pigment-filled phagocytes and scattered erythrocytic debris. The changes were similar to those observed in the third experiment and less marked than those observed in the fourth. Iron and fat were absent as in the fourth experiment. The kidney resembled that in the fourth experiment except that there were no interstitial collections of cells. There was more iron, but no fat was seen in sections stained with scarlet red.

Comment on Experiments 1 and 2.—Our studies showed that the lesions found were restricted to the spleen, liver and kidneys. The spleen observed in the second experiment was small and fibrotic and showed definite changes of hyaline perisplenitis which were not present in the spleen observed in the first experiment. This was probably incidental with no bearing on these experiments. The liver observed in the first experiment showed scattered small collections of lymphocytes. These were not present in the liver studied in the second experiment and their significance is indeterminate but probably also incidental. There were small subcapsular hemorrhagic areas in the liver in the second experiment. These were so recent that phenylhydrazine as an etiologic factor can readily be dismissed. In general, observation of livers in both experiments showed them to be remarkably normal. There were large scars in the kidneys in the first experiment and smaller ones in the kidneys in the second experiment. These contained some fibrous tissue which appeared to be of recent formation. The tubules in the scars were profoundly affected, but the glomeruli were practically spared. The scars are not true infarcts but their situation and shape are strongly suggestive of a vascular rather than an ascending infectious origin. They resemble closely some of the scars found in the kidneys of elderly human beings with arteriosclerosis which are presumably due to slow progressive ischemia. Although iron occurs normally in small amounts in the spleen and liver of normal dogs, it was definitely increased in these experiments, doubtless the remains of larger amounts deposited during periods of active destruction of blood. Detailed study was made of the blood vessels, particularly the arterioles, in all the histologic material examined and we finally concluded that there were no significant changes in the media or intima and no increase in the periarterial connective tissue. We are of the opinion that none of the abnormal findings in these two experiments was due to the phenylhydrazine itself, except the evidence of the destruction of erythrocytes and hemoglobin.

Comment on Experiments 3, 4, and 5.—The pathologic anatomy observed in the third experiment may be summarized as follows: (1) evidence of hemolysis and hemoglobin destruction; (2) hemorrhagic areas in the omentum possibly due to hemolysis or to toxemia; (3) marked reduction in leukocytes of the spleen; (4) atrophy of the parenchymal cells of the liver, and (5) overloading the convoluted tubules of the kidney with iron. Much of the iron in the liver and spleen of this dog was in a rather diffuse form, apparently it was being produced much faster than it could be phagocytosed. In the kidney the tubular epithelium and possibly the glomeruli also were apparently excreting the iron but it was piled up in the tubules, probably much more rapidly than it could be taken care of. Observations in the fourth and fifth experiments confirm this phenomenon in the kidneys and show changes in

the liver similar to those observed in the third experiment except that iron was absent. An observation which is difficult to evaluate is the rather extensive interstitial inflammatory reaction in the kidney in the fourth experiment particularly since nothing similar was found in the kidneys in the third and fifth experiments. This change might occur directly as a result of phenylhydrazine but its localized inflammatory nature and the absence of such a lesion in the third and fifth experiments suggest that it is an incidental observation. The atrophy of the liver is probably a direct result of the large doses of phenylhydrazine either by direct toxic action or by pressure from capillary spaces hugely engorged with disintegrating erythrocytes and large phagocytic cells.

SUMMARY

Two dogs were given 146 daily doses of phenylhydrazine hydrochloride in a period of eight months in amounts sufficient to produce an effect on the erythrocytes comparable to that desired in the clinical use of phenylhydrazine. The total dosage, calculated on body weight, was equivalent to that necessary in the treatment of the usual case of polycythemia vera for from four to six years. Necropsy and histologic examination four and five months, respectively, after phenylhydrazine had been withdrawn and twelve and thirteen months after the beginning of the experiments showed nothing abnormal which could be definitely attributed to phenylhydrazine, except increased deposition of iron in the liver and spleen.

One dog was given doses of phenylhydrazine which were lethal in six days. The only significant evidence which could be definitely attributed to phenylhydrazine, per se, was that of rapid destruction of erythrocytes and hemoglobin, atrophy of the parenchymal cells of the liver, reduction in the number of the splenic leukocytes, and overloading of the cells of the renal convoluted tubules with iron. Partial necropsy on two dogs given similar doses showed the same changes in the liver and kidneys.

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Tetany and Chronic Diarrhea*

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THE infrequency of tetany as an accompaniment of diarrhea is attested by the fact that most contemporary writers on tetany rarely discuss diarrhea as an etiologic factor. The subject is barely mentioned by MacCallum, and Dock and Lisser. Barker describes "tetania colonica" which he says may be produced in predisposed persons by dilatation and obstruction at any point in the intestinal tract. Critchley, in reviewing the pathogenesis of tetany, speaks of the intestinal and colonic types of the syndrome, and enumerates certain recorded causes. Trousseau, in his celebrated lecture on tetany, in which the sign bearing his name is described, states that, "of the pathologic conditions (causing tetany) diarrhea, especially when abundant and chronic, is the one which exerts the most striking influence." He cites the frequent occurrence of tetany during the cholera epidemic of 1854 in support of this contention. However, if one is to judge by the literature, diarrhea is one of the least common causes of tetany in the adult. A few reported cases and certain recent experimental studies cast some light on the subject. We propose here to report a case of tetany of this type, to review the literature concerning it, and record the results of treatment by parathormone.

A married woman, aged thirty-one, who had resided in northern Wisconsin all her life, came to the Mayo Clinic in June 1927. She was one of a family of ten children; her parents and all her brothers and sisters were alive and well. Her general health had been fair except for an attack of influenza in 1920, and tonsillectomy performed during the same year. However, she had always been small and rather frail, and had suffered occasionally from diarrhea since early childhood. In 1920, she had noticed that in using a pencil her fingers became cramped and stiff and that in walking rapidly her legs cramped, but she regarded these symptoms as of little importance. She was married in 1921, and one year later, during the fourth month of pregnancy, tingling and numbness of the hands with marked stiffness of the muscles of the right arm developed. She recalled having had a definite carpal spasm at this time lasting about six hours. During the next two weeks she had three similar attacks. The pregnancy terminated in stillbirth at eight months. She recovered her usual health slowly during the following year. In 1923, at long intervals, definite but mild spasms occurred in the muscles of the hands. She had always suffered more or less from flatulence and abdominal distress, particularly after the ingestion of fat food. At intervals since 1922 she had had rather severe attacks of diarrhea lasting about two weeks; in describing these attacks, she mentioned that diarrhea brought on the attacks of tetany. In 1926 she had suffered from vomiting and diarrhea for

*Submitted for publication February 9, 1928.

nearly two months; she lost 20 pounds in weight and while she noticed some stiffness and numbness of the hands there was no definite tetany. In April 1927 an attack of diarrhea was followed by paresthesia, numbness, and stiffness of the hands and she was totally incapacitated. Shortly afterward definite carpal spasms developed which finally brought her to the clinic. In giving the history the patient was inclined to lay great stress on the gastro-intestinal disturbances, and was convinced that they were responsible for the peculiar numbness and cramping of her hands.

The patient was 5 feet in height and weighed 76 pounds. The systolic blood pressure was 82, and the diastolic 60. Temperature, pulse, and respiration were normal. There was slight darkening of the skin over the exposed areas of the body; the mucous membranes were not pigmented and there was no accentuation of the pigment over the malar surfaces and the forehead. The most striking symptom was the carpal spasm which appeared spontaneously at various times during examination. Examination of the heart, lungs and abdominal and pelvic organs was essentially negative, as was the ophthalmologic examination except for slight horizontal nystagmus. Slight marginal glossitis was noted but there were no other oral lesions. Neurologic examination was objectively negative except for strongly positive Chvostek's and Trousseau's signs. Difficulty was encountered on attempting to study the electric reactions, the patient's hand going into tetany as soon as the electrode was placed on the ulnar nerve. Urinalysis was negative. The blood Wassermann reaction was negative. The hemoglobin was 75 per cent, the erythrocytes numbered 4,000,000 and the leukocytes 7,000. The differential count was negative except for a slight relative increase in lymphocytes (27 per cent). A test meal showed free hydrochloric acid 34, and total acidity 50. The stools contained fat but no parasites or ova. Roentgenograms of the spine were negative; stereoscopic plates of the chest showed a healed tuberculous lesion of the right upper lobe. The volume index of the blood was 0.87. Two blood calcium readings showed 6.3 mg. and 6.7 mg. for each 100 c.c.

Being somewhat at a loss to explain the cause of the tetany, we urged the patient to go to the hospital for further study. She was unable to stay, however, and was dismissed with instructions to follow a high vitamine diet and to take cod-liver oil. She was also given desiccated thyroid, 1 grain daily, and calcium lactate in teaspoonful doses three times a day.

At the end of a month she wrote that she had gained 10 pounds in weight, had been free from tetany and paresthesia, and in general had been doing well except for flatulence and mild epigastric distress after meals. In September a letter stated that she had suffered from severe diarrhea all of the month of August and had lost about 5 pounds in weight. There had also been mild carpal spasms and rather annoying paresthesia of the hands. Menstrual periods had been irregular and scanty and the patient raised the question of possible pregnancy. She wrote again in October to tell us that all previous symptoms had recurred and with more severity. A generalized convulsion had occurred with marked spasms of the hands and feet but without loss of consciousness. A week later there were three attacks in one day. She described these as very painful, and associated with great difficulty in speech and in swallowing. She had lost 12 pounds in weight and she had not menstruated since August. She returned to the clinic October 24, and was admitted to hospital for observation and treatment.

The patient was found to be in much the some condition as on the previous visit. The blood pressure was still low, 86 systolic and 56 diastolic. Ferenczi-Poole's, Chvostek's, and Trousseau's signs were present. The hands went into the obstetric position after slight increase in respiration which is necessary for an examination of the chest. A gynecologist reported the pelvic organs to be normal; no evidence of pregnancy was found. The patient again emphasized the relation of diarrhea to the attacks of tetany

and said that she was sure she could get along without trouble if her digestion and bowels were in better condition.

The laboratory examinations were all repeated with negative results except that the blood calcium was low, 7.1 mg. for each 100 c.c. There was moderate secondary anemia; the hemoglobin was 54 per cent, erythrocytes numbered 3,600,000 and the leukocytes 7,500. The blood urea was 18 mg. for each 100 c.c., and the carbon dioxide combining power of the blood plasma 48 volumes per cent. Roentgenograms of the stomach, sella turcica, spine, gallbladder, and colon were negative. The diarrhea which had begun during the previous month had subsided somewhat, but there were still one or two large offensive fatty gray stools daily: the stools were not foamy at any time. The high content of fat in the stools was confirmed by chemical and microscopic examinations. A careful search for parasites and ova was made with negative results. Two groups of stool cultures with taurocholic acid medium were negative for *Monilia psilosis*. The basal metabolic rate on two occasions was +12 and +10 per cent. After a period of observation it was felt that the patient's contentions in regard to the relation of diarrhea to the tetany were probably correct. She was able to recall an attack of diarrhea preceding all of the major and most of the minor attacks of tetany, the one exception being the attack which had occurred during pregnancy. It was suggested that either pancreatic infantilism or sprue might be the etiologic factor. The latter could not be definitely confirmed in the absence of Monilia in the stools, although there was much to suggest it. The theory of infantilism seemed to rest on somewhat better grounds, in view of the history of diarrhea and undernutrition since early life. Because of the possibility of pancreatic disease, a test for glucose tolerance was made with results as follows: fasting blood sugar 90 mg. per cent; the blood sugar a half hour after 100 gm. of glucose was given was 99 mg. per cent, after one hour 68 mg. per cent, and after two hours 82 mg. per cent. This seemed a rather abnormally high tolerance, although diminished absorption from the intestine could not be excluded.

The patient was placed on treatment consisting of high-calcium, high-vitamine diet, 1 dram of calcium lactate, three times a day, and 15 units parathormone on alternate days. Under this regimen the blood calcium rose rapidly to normal and the symptoms and signs of tetany disappeared; the patient gained in weight and felt well, although she still suffered from flatulence and epigastric distress after meals. The electric reactions were checked three days after the first dose of parathormone, at a time when the blood calcium was 9 mg. for each 100 c.c. The cathodal closing contraction occurred at 0.5 milliamperes and the cathodal opening contraction at 3.5 milliamperes. These figures represented improvement so far as the tetany was concerned. The anemia also improved, the hemoglobin rising to 63 per cent (Dare) and the erythrocytes to 4,120,000. Since the gastro-intestinal symptoms were still troublesome and because of the probability of deficient fat absorption a change to a high-protein, high-vitamine diet was made shortly before the patient's dismissal; this resulted in practically complete relief of abdominal symptoms. As might have been expected, however, the serum calcium fell somewhat. At the time of her dismissal she was instructed to continue the high-protein diet with 10 units of parathormone on alternate days, and calcium lactate in the dosage given previously.

A letter received three weeks after the patient reached her home was very encouraging. She had gained 7 pounds and there were no signs of tetany. She had suffered slightly from flatulence. A blood calcium determination at the Children's Hospital in Milwaukee was reported as 11.3 mg. for each 100 c.c. The last report was received two and a half months after dismissal. Her weight was 93 pounds, a gain of 15 pounds, and she was well satisfied with her progress; she said she felt very much better and stronger than she had for some time. She had menstruated normally in December and

in January. December 26, 1927, the blood calcium was 11 mg.

During the month of January the patient had suffered from a mild recurrence of diarrhea and had noticed paresthesia of the extremities. January 26 the blood calcium was 7.84 mg. She was still somewhat troubled by flatulence although less than before. The use of pancreatin had eliminated most of the indigestion and postprandial distress. She was advised to increase the dose of parathormone from 10 units to 15 units on alternate days and to eliminate all fat from the diet until the diarrhea subsided. It was also suggested that the dose of parathormone be reduced later, when the blood calcium had returned to a normal level.

Comment

The features of this case meriting special discussion are (1) the chronic recurring diarrhea followed by tetany, (2) the striking constitutional and nutritional defects, and (3) the prompt response to treatment with parathormone. As has been stated, the production of tetany by chronic diarrhea is not a common occurrence in the adult. Sonrier (1877) reported the case of a woman who suffered for six years from recurrent diarrhea; for two years these attacks had been followed by severe tetany. He was unable to explain the condition satisfactorily, but mentioned the "celiac flux" described by Trousseau as a possible factor.

Griffith, reviewing the subject of "Tetany in America" (1895) noted only two cases of this type. The first, (Mills, 1879) was that of a girl aged sixteen, who, following rheumatic fever, suffered from diarrhea which was in turn complicated by moderately severe tetany. The whole process was of short duration, and symptoms were relieved by the administration of silver nitrate pills and opium. The second case (Stewart, 1889) was that of a man, aged thirty-nine, who for eight years had suffered from tetany. Stewart stated: "During the intervals of freedom from attacks he suffered from diarrhea which moderates when the tetany makes its appearance." Howard (1906) reported nine cases of tetany, one of which was associated with diarrhea. The patient was a man aged twenty-four, who had acquired the intestinal disorder while in the South. Howard stated that this was the only report of tetany in the adult of purely intestinal origin which had appeared in American literature for a decade. He cited two cases of tetany caused by gastroenteritis (Strong 1902, and Brown 1902) and mentioned iRegel's report of tetany associated with helminthiasis. In the British literature of the period, one finds a report by Thomson (1904) of a case of chronic pulmonary tuberculosis and marked "mucomembranous colitis" in which tetany developed with the patient was under his care. The patient recovered ultimately from both colitis and tetany.

The association of tetany with sprue, first recorded by Bassett-Smith (1910) is the first instance we have been able to find in which tetany was definitely connected with a particular type of intestinal disorder in the adult. Bovaird (1921) reported a series of thirteen cases of sprue with two of which tetany was associated. Barach and Murray (1920) reported one of Bovaird's cases in greater detail, giving figures for the blood calcium. In this case, which was typical of severe sprue, the blood calcium was 6.5 mg.

for each 100 c.c. and curiously enough was not elevated by intravenous calcium medication. Scott (1925) stated that low "ionic" calcium was a constant accompaniment of sprue, and mentioned the occurrence of tetany in severe cases. His patients showed little or no reduction in the total blood calcium; however, the method he used for the determination of ionic calcium, that of Vines, has not been generally accepted.

Among the other reported cases of diarrhea associated with tetany are those of Gibson (1923), Tileston and Underhill (1923), and Siffredi and de Rabinovich (1925). In both of the latter cases calcium studies were made; in Tileston's case fatty diarrhea had existed for six months associated with typical tetany and blood calcium of 6 mg. The cause of the diarrhea was not determined; metabolic studies, however, showed a tendency to calcium retention, excessive excretion of ammonia without other evidence of acidosis, and poor utilization of fat. In Siffredi and de Rabinovich's case the blood calcium was 8.3 mg. and the intravenous administration of calcium chloride promptly relieved the attacks of tetany. Among the most extraordinary cases of the kind on record are those of Blumgart, who described three patients suffering from asthenia, diarrhea, and anemia, one of whom died after an attack of tetany, the blood calcium being 5.3 mg. for each 100 c.c. The chief clinical and pathologic finding in Blumgart's cases was the malabsorption of fat; the small intestine was covered with punctate grayish elevations which histologically showed collections of phagocytes loaded with fat.

The association of tetany and diarrhea in infants is much more common and since, in our case, there was evidence of gastro-intestinal disturbances dating from childhood, it is interesting to note the recorded cases. Langmead (1911) described fourteen cases of "relapsing tetany" associated with dilatation of the colon and abnormal and offensive bowel movements. These cases all occurred in children and in describing the patients he says, "The general growth and development was always retarded, the patients being thin, wizened and undersized." He comments on the resemblance of these cases to the cases described by Herter. Lichtenstein described the stunting of growth and physical retardation occurring in celiac disease; in four of his nine cases actual tetany was also present. It is not definitely known how late into adult life such intestinal disorders may persist (probably only until puberty) but a case described by Findlay and Sharpe suggests a relationship between celiac disease in infancy and tetany in the adult. They recount the case of a young woman who had suffered from celiac disease in infancy in whom recurring diarrhea developed in later life, and who subsequently had tetany. She had always been undernourished and underdeveloped, her maximal weight being six stone (84 pounds). The striking similarity to our case is apparent; Tileston and his associates also state that the case they reported was essentially a duplicate of that reported by Findlay and Sharpe.

The infrequent incidence of tetany in association with the relatively common symptom of diarrhea points to the possible existence of a predisposing cause. While tetany has been described as a complication of certain infectious diseases (notably typhoid fever and cholera) it is apparently rare in bacillary dysentery and amebiasis. Logan and Bargen in their extensive experience with chronic ulcerative colitis have only observed one case associated with tetany. There have been cases reported under the indefinite diagnosis of "gastro-enteritis," and Loeper and Béchamp have found a low calcium content of the blood in this condition. Nevertheless, many of the reported cases in which diarrhea and tetany were associated have been complicated by constitutional or nutritional defect. The present knowledge of nutritional disorders and disturbances of the glands of internal secretion is too fragmentary to justify extensive hypotheses with regard to these defects, although the evidence bearing on their relation to tetany is of considerable significance. The common factors in the group of cases in which tetany and diarrhea are associated seem to be: (1) malnutrition and physical retardation, (2) recurrent diarrhea associated with deficient fat utilization, and (3) disturbance in calcium metabolism. The coexistence of these factors suggest at once either sprue or intestinal infantilism (Heubner's "schwere Verdauungsinsufficienz"). As we have stated, our case presented such striking evidence of retarded development as to raise the question of pancreatic or intestinal infantilism. These rare conditions are differentiated only with difficulty, and will probably remain unclassified until methods of studying pancreatic and intestinal digestive functions are perfected. Bramwell first described the pancreatic variety, and since then cases have been recorded by Rentoul, Clarke and Hadfield and others. Necropsy in Clarke and Hadfield's case showed an atrophic pancreas and chronic inflammatory changes in the colon. In none of the recorded cases was tetany associated. Herter (1908) described "intestinal infantilism," the clinical features of which are similar to those of celiac disease; in fact, Miller is inclined to regard both pancreatic and intestinal infantilism as varieties of the latter disorder. Strauch's description is excellent and applies to the entire group; "The principal factor is a very severe chronic intestinal insufficiency with much reduced function of the digestive glands, which is rather refractory to treatment and as a rule affecting children beyond the stage of infancy. The tolerance for fats and carbohydrates is reduced so that slight dietary indiscretion or a minor parenteral infection brings on a digestive disturbance of severe nature with marked loss of body weight and a reparability of function far below normal. But also without such recognizable causes obstinately relapsing diarrhea of a fermentative character will occur. In addition, or rather as a consequence of this, the somatic development becomes seriously impaired and finally the children are set back in body weight and height by years."

The occurrence of tetany in celiac

disease has already been mentioned (Lichtenstein), and its possible relation to tetany in the adult recorded (Findlay and Sharpe). In a recent review of Levinsohn, the increased loss of calcium in celiac disease is discussed; this is explained on the basis of either increased excretion or failure of resorption. He refers to the frequent association of tetany, which he regards as of the parathyroprivic type; necropsy reports describing atrophy and fatty degeneration of the digestive and endocrine glands are also cited. It therefore appears that either celiac disease or certain closely related conditions may be a factor in producing infantilism, fermentative diarrhea and constitutional defects, thus furnishing a possible background for tetany in later life.

Since sprue is the diarrheal disease of adults in which abnormal calcium metabolism and tetany occur most frequently, it is of interest to note the hypothesis of its etiology advanced by recognized authorities on the subject. Ashford regards physiologic glandular deficiency as one of the antecedent causes, stating that this deficiency involves the digestive glands and the glands of internal secretion. He also describes the symptoms of the condition, mentioning loss of weight, asthenia, constipation alternating with soft fermented stools, pigmentation of the face, vague myalgia, cramps in the limbs, and psychic irritability. The low blood calcium values noted in sprue have already been mentioned; Ashford and Hernández find that the blood calcium is below the normal level in sprue and in the nutritional disturbances which constitute its major predisposing cause.

These observations on sprue furnish an interesting sidelight on the relation of tetany to diarrhea, and raise the question of whether our case and certain of the other recorded cases of colonic tetany were not actually sprue. The question unfortunately cannot be answered positively; Blumgart did not believe that his patient suffered from sprue, and in our case the diagnosis could not be established, in view of the patient's lifelong residence in the North and the absence of Monilia from the stools.

It must be remembered that certain obscure forms of tetany are on record in which there is evidence to show that parathyroid deficiency is present as a part of generalized endocrinopathy. In such persons, a variety of circumstances might precipitate an attack of tetany. Morawitz describes a boy of seventeen with infantilism, delayed growth of bone, and swelling of the salivary glands, who developed tetany after a fall at the age of seven. Woltman, in his discussion of a case of tetany in a eunuch with signs of polyglandular disease, mentions the theories of Falta and Weisel; they refer to multiple endocrine sclerosis due to a connective-tissue diathesis, as an expression of a generalized constitutional defect. Whether our patient suffered from a generalized endocrine defect, intestinal infantilism, or atypical sprue cannot be decided definitely without further observation and improved methods of study. It is of interest to note that probably latent tetany had been present for years (the

carpal spasms during pregnancy are suggestive of this), and that other evidences of endocrine disease were present as well.

Much experimental work has been done on the relation of the intestinal tract to tetany, the greater part of it having a direct bearing on the cases under discussion. The numerous studies on calcium metabolism in rickets with relation to diet, fats, fat-soluble vitamine, and the reaction of the intestinal contents are noteworthy and illustrate the difficulty of studying this problem. In most cases the clinical association of tetany and diarrhea depends, as we have stated, on disturbed calcium metabolism. Barach and Murray, in explaining the occurrence of tetany in sprue, state that the phenomenon depends on deficient calcium absorption, as well as increased calcium excretion through the colon; they cite von Noorden's view, that calcium is absorbed in the upper part of the intestine chiefly as the soaps of fatty acids, and therefore believe that calcium absorption must be interfered with in sprue, since this disease is associated with defective utilization of fat. This explanation would seem to hold also for intestinal infantilism. Holt, Courtney, and Fales have reported on the relation of fat in the diet to calcium absorption in children; they find a very low degree of calcium utilization in diarrhea and in chronic intestinal indigestion.

Dragstedt and Peacock studied the influence of diet in thyroparathyroidectomized dogs, and found that diets rich in lactose and dextrins prevented tetany, while meat diets precipitated attacks; constipation also brought on tetany. Swingle and Wenner, in discussing the effect of the feeding of strontium in preventing tetany, stated that dietary factors, strontium administration, magnesium lactate and intravenous Ringer's solution prevent tetany by reducing the permeability of the intestine to calcium, and thus prevent loss of calcium through the colon. They believe that constipation and meat diets cause an increase of certain unnamed end-products of protein metabolism, which increase the permeability of the intestinal wall, causing increased calcium excretion and subsequently tetany.

Even more important observations on the relation of tetany and diarrhea are those of Luckhardt and Compere, who have shown that thyroparathyroidectomized dogs who have been kept free from tetany by the administration of calcium, can be thrown into tetany by drastic purgatives; these results are also explained on the basis of increased permeability of the intestine to calcium. Stewart and Percival, in their recent experiments, seem to furnish conclusive proof that the large intestine is the main excretory route for calcium, a point which further emphasizes the etiologic importance of diarrhea in the production of tetany. The occurrence of tetany in diarrhea, therefore, may be due to deficient calcium absorption, dependent on partial failure to utilize fat, or too rapid acceleration of the intestinal contents; probably both factors are important. There is possibly also increased calcium excretion through the colon due to changes in permeability. This relatively simple

explanation, however, probably does not account for all cases of intestinal tetany; factors such as the diffusibility of calcium, and its relation to other inorganic salts in the blood and tissues may be of fundamental importance. A case now under the care of Logan and Bargen illustrates how much is yet to be learned of the chemistry and physiology of tetany. In this case, in which colectomy and ileostomy have been performed for severe chronic ulcerative colitis, typical tetany develops without any change in the blood calcium, in consequence of obstruction to, or profuse discharge from, the ileostomy opening. In this case the relation of the intestinal tract to the production of tetany is very different from that in the case we are reporting. It emphasizes the possible variations and difficulties in the explanation of the problem. A study of this case now in progress may cast much additional light on the whole subject.

The introduction of parathormone by Collip has furnished the medical profession with a substance to control maternal, postoperative, and infantile tetany by its effect on the blood calcium. Its use has been reported in the treatment of sprue; in this disease Ashford and Hernández find that it elevates the blood calcium and controls the muscular "cramps," thus proving the latter to be a manifestation of latent tetany. These writers regard parathormone as an important adjunct to the dietary treatment of the disease, rather than a curative measure. Baumgartner also reports elevation of blood calcium in sprue after the use of parathormone but raises the question of its possible effect on calcium reserve. In our patient there was marked general improvement (possibly due to dietary factors), relief from tetany, and a definite effect on the blood calcium. Although a high-protein diet and an attack of diarrhea lowered the blood calcium slightly in spite of parathormone administration, the tetany level of blood calcium was not reached, and the patient had no noteworthy symptoms. Figure 1 shows the blood calcium and phosphate levels during the period of observation with reference to diet and the medication employed.

The method by which parathormone acts on calcium metabolism is still under discussion. The experiments of Stewart and Percival indicate that this substance does not affect the rate of calcium absorption from the intestine, nor the rate of calcium excretion from the colon. It is probable, therefore, that the use of parathyroid hormone in colonic tetany is symptomatic treatment, and that attention to the underlying nutritional and constitutional defect is of primary importance. However, in our case it was impossible to accomplish anything until the tetany was under absolute control, and in this connection parathormone was invaluable.

There are numerous hypotheses with regard to the effect of parathormone on the calcium of the blood serum; Cantarow, Caven and Gordon believe that it acts by retarding the precipatation of calcium from the blood (that is, in osseous tissue) and by actual abstraction of calcium from the skeleton. Stewart and Percival suggest that the parathyroid hormone con-

trols the distribution of calcium between the blood and the tissues, by regulating the proportion of total serum calcium which is readily diffusible. Greenwald and Gross believe that the parathyroid hormone is the substance which keeps in solution the excess of calcium phosphate which Holt, LaMer, and Chown have shown to be present in the blood; or the hormone may be necessary for the preparation of this substance. It is generally agreed that the elevation of serum calcium produced by parathormone is brought about by the loss of calcium from the skeleton. The experiments of Greenwald and Gross and those of Hunter and Aub established this point definitely. It must be appreciated, therefore, as has been pointed out by Greenwald and Gross, and others, that the use of parathormone does not improve calcium assimilation but rather causes increased mobilization of calcium from the skeletal reserves, and that it is necessary to protect the reserves when employing parathormone in treatment. In a case such as the one we have reported it is necessary to supply calcium in the diet as calcium lactate, to insure an adequate supply of fat-soluble vitamine, and to keep in mind the benefi-

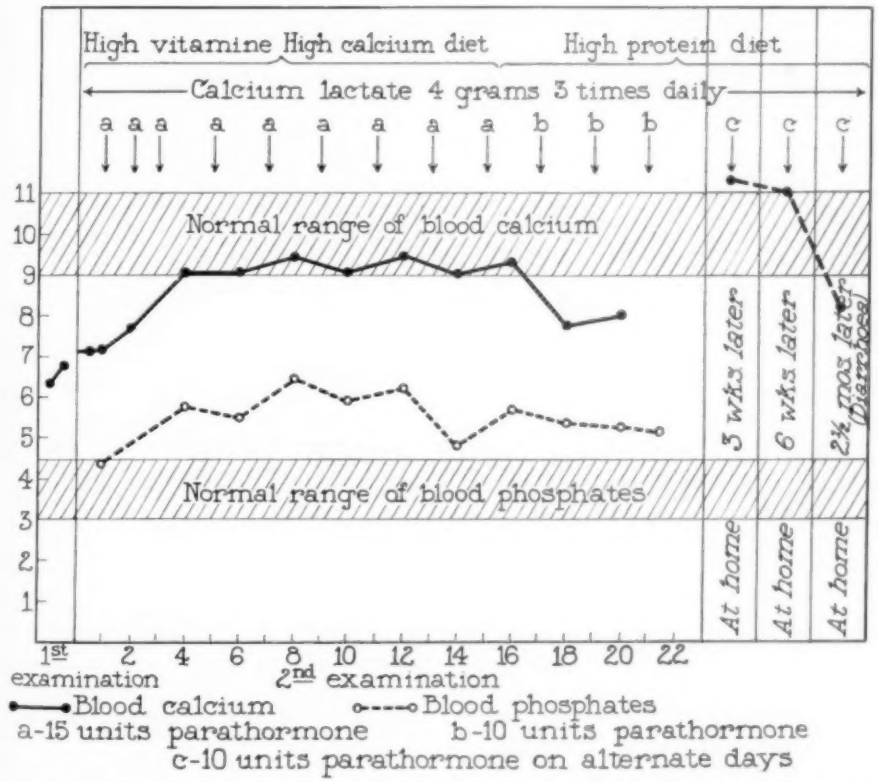

FIG. 1. The effect of treatment with parathormone and calcium lactate on the calcium of the blood serum in a patient with tetany due to chronic diarrhea.

cial effects of sunlight and ultraviolet irradiation on calcium absorption.

Summary

A case of tetany due to diarrhea of obscure origin with nutritional and constitutional defects is described. The occurrence of related cases in the literature and the possible relation of this syndrome to sprue and intestinal infantilism is considered. The experimental evidence showing the relation of the intestinal tract to tetany, and the possible influence of altered intestinal permeability on calcium absorption and excretion is discussed.

The therapeutic response in this case to the administration of parathormone and calcium lactate was striking, as shown by symptomatic improvement and by the behavior of the serum calcium. In view of the possible calcium depletion by parathormone, the necessity of adjuvant measures to protect the calcium reserve is emphasized.

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The Significance of Ureteral Stricture in Relation to Abdominal and Other Symptoms

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STRICTURES of the ureters have been known to the urologist since the early days of ureteral catheterization. In 1902 Howard Kelly expressed the conviction that stricture of the ureter was a very real entity, often leading to mistaken diagnoses and an erroneous conception of the etiology of some renal diseases. It remained for Hunner to prove in them a source of trouble, often quite remote from the lesions per se, hitherto ascribed to disorder or pathology of other structures. Why the ureter, an essential unit in the body's drainage system, lined with a sensitive mucosa and highly vascularized, 30 cm. in length and subject to pressure, distortion, injury, as well as the constant possibility of conducting and being infected by material from the kidney or bladder, has escaped more careful scrutiny, is an unanswered question, and a challenge to clinician and urologist alike. It has not been an easy matter to establish in the medical mind the far reaching importance of stricture as the point of origin of so diversified a symptom-complex as is often easily proved to exist by the measure of relief which so frequently follows appropriate treatment of the narrowed area. The effects of kinks and ptoses while often causative of similar manifestations should not be considered in this connection.

Women are apparently more frequently affected than men although it is possible that with increasing knowledge the disproportion in incidence may be less striking. The relative number of male and female patients which make up the clientele of each individual observer must also be taken into account.

Pathological investigations have furnished ample support for the establishment of ureteral stricture as an entity. Howard and LeCocq examined the ureters at fifty routine autopsies and found stricture and ureteritis to be extremely common. Eisendrath, Goldstein, Hunner and others have added records of gross and microscopic studies which are most convincing.

Strictures are caused by congenital and acquired influences. The latter group comprises by far the larger number and two main factors—focal infection and traumatism—are the preeminent causes. Foci of infection any-

where in the body, but especially those so commonly found about the head, may safely be assigned a major role. Other infections, of seeming local significance only, must also be reckoned with as possible etiologic factors. The infectious diseases are undoubtedly causative of narrowing at times, as proved, or at least very cogently suggested by a history of disturbance, perhaps of intermittent manifestation, occuring in the years which follow. Periureteritis with infiltration of the ureteral wall may follow or occur coincidentally with inflammatory processes in the immediate vicinity of the ureter. Penetrating injuries of the abdomen, by anyone of several agents, or traumatism resulting from operative procedures, wherein the operative field includes or lies in close proximity to the ureter, may serve as causes of obstruction, partial or complete, depending upon the extent of the injury. Hunner cites a group of cases occuring as sequelae to the reactionary inflammation incidental to the use of the cautery and radium in the treatment of pelvic neoplasms.

The symptomatology in one group of cases directs attention at once to the kidney-ureter-bladder tract, the manifestations being those of renal or ureteral colic. Sudden occlusion from edema of the strictured area is the probable explanation for the appearance of such attacks. Such cases are likely to receive the benefits of early catheter investigation, but unless the possibility of stricture plus edema is borne in mind as a cause, a report of essentially negative findings may be returned. In any case the dilatation incidental to the catheterization often brings the desired relief. In another and much larger group the symptomatology is often most diversified and without painstaking study may appear to bear no relationship to the urinary tract. It is usually possible to elicit some complaint, often considered by the patient as a very minor or inconsequential phase of his ailment, which is subjectively related to the bladder. The most frequent symptom is frequency of varying degree; again dysuria mild or severe or a combination of the two. Frequency is often alleged to be a direct result of nervousness, but by and large, individuals with a normal urinary tract do not so react when under the influence of nervous strain. Dysuria, when present, varies in degree from a slight burning, often hardly sufficient to attract attention, to actual pain. Incontinence has been reported as an outstanding symptom in some instances: in our series three patients complained of a definite lack of control. In this connection we are impressed with the belief that the prolonged incontinence often seen in childhood may, in at least a portion of the instances, be dependent upon an unrecognized or unsuspected ureteral stricture. Any or all of these symptoms may result from a cystocele with its attendant cystitis and this fact must be taken into account in the making of a differential diagnosis. Moreover it must not be forgotten that the two conditions may exist coincidentally.

Painful coitus is a not infrequent complaint from which complete relief has been experienced in a number of instances by the dilatation of a stric-

ture at or near the pelvic brim. The rather close anatomic relationship between the upper third of the vagina and the lower ureter together with the changed conditions incidental to the act is the probable explanation for the pain. Abdominal manifestations varying from diffuse pains to symptoms referable to one or more of the contained viscera are frequently encountered. A chronic appendicitis is perhaps diagnosed in error more often than any other condition and it is safe to say that large numbers of appendices have been removed without relief of symptoms which were on the contrary due to a strictured ureter. It is quite possible that the appendix serves at times as a focus of infection which may be causative of ureteral pathology, but this, we believe, is infrequently the case. Physical evidence of gall bladder dysfunction or pathology has been observed to disappear entirely following the discovery and appropriate treatment of a right-sided stricture. This phenomenon has been so striking in its frequency of occurrence that we feel justified in recommending ureteral catheterization, especially an investigation of the right side, as a preliminary to operations upon the gall bladder. In many instances we have found pathogy in both places and in several the lesions have been so sufficiently advanced that the correction of one would have rendered the patient a measure of benefit not at all commensurate with justifiable expectations. Gaseous distension of the hollow viscera and disturbed function of the colon, quite often diagnosed as a colitis, have in several instances been traced in the last analysis to ureteral pathology. Extra-abdominal symptoms such as persistent headaches, thoracic pains of varying distribution, pains in the lower extremities, low grade temperatures, often of daily recurrence, peculiar mental reactions, etc., have been met with. The manifestations enumerated find their explanation in toxic and reflex influences. Evidences of a low grade nephritis, a result of back pressure and infection acting singly or in conjunction with each other, have been observed to disappear with the relief of stricture. A lack of endurance is an outstanding feature in practically all cases.

The disability which arises from this condition is often very great in proportion to the size of the lesion. Not infrequently one encounters a patient who in his search for health has not only been treated medically for years but quite often has undergone one or more laparotomies and all without benefit. Many have been classified as chronic neurasthenic invalids whilst others have been looked upon, especially by many physicians who have been years in practice, as nuisances or pests. One's faith in the virtues of the healing art becomes rehabilitated and refreshed when one of these patients, whose complaints have been legion, states without reservation that he is well.

The diagnosis is usually established from the history but often a most searching inquiry must be made into details, lest seemingly inconsequential or trivial symptoms are passed over as meaningless. The physical examination is in some instances most convincing in its pointings but on the

other hand it may yield little or nothing that is helpful. Painstaking care is required in the evaluation of findings and the possibility of the existence of a stricture calling weakly for recognition must not be lost sight of when the findings seem vague and more or less obscure. Tenderness high in the kidney angle can usually be found but several instances have come to our attention in which it has not been present. Heavy percussion with the fist will occasionally bring it out when direct pressure fails. As the ureter crosses the pelvic brim between McBurney's point and the umbilicus, usually nearer to the latter, pressure at this point will usually call forth in stricture patients localized or referred pain. Occasionally a similarity to a distress included in the list of ailments will be recognized at once and commented upon. The discomfort may be referred upward to the epigastrium or to one or the other kidneys or downward to the bladder or to the vicinity of one or the other ovaries. A desire to void may be experienced and heed should be taken of this even though it is very slight. The point just mentioned may be the site of the maximum tenderness and pressure above or below this will evoke a discomfort of lessening intensity only. In the event that the appendix overlies or is fixed in close proximity to the ureter and is itself sensitive to pressure a fine discrimination will be required to separate the response from each structure, if it is at all possible to do so in an individual case. In women the bimanual examination of the pelvic structures is relatively easy and the lower ureteral zone—not the ureter per se—can be readily palpated. Again, pain or discomfort may be referred to any part of the kidney—ureter—bladder tract. Attention should be directed to the fact that the ureter lies in close proximity to the anterior aspect of the sacro-iliac joint at and just below the pelvic brim and pressure at this point may call forth pain from an arthritis rather than from stricture. Examination of the back should also be made to prevent this error, bearing in mind that the two conditions may co-exist.

It is quite natural to assume that the examination of the urine should disclose information of value; in a portion of the cases this is true while in the great majority the findings are either of a quasi-suggestive nature or entirely negative. Hunner's statement in respect to this phase of the examination is quite comprehensive in its details—"In 20 per cent of stricture patients, there is a chronic pyelitis on one or both sides, and the urine will give characteristic findings. In 50 per cent only a few erythrocytes, a few leukocytes, albumin from a slight trace to large quantity, or casts, or a combination of these elements will be found. Too often in the past such evidences of disease, when found in meager quantity and only on the most painstaking urinalyses, have been considered as of no significance. In the remaining 30 per cent of stricture cases, the urinalysis is completely negative and patients in this group may present symptoms strongly pointing to the urinary tract and yet be sent to the gastro-enterologist, the orthopedist, or the explora-

tory laparotomist for a diagnosis simply because of the negative urinalysis." To this should be added, that in the female especially, deductions should be made from the examination of catheterized specimens only. The reason for this is obviously to eliminate a vaginal or urethral source of contamination.

The modus operandi by which stricture damage is wrought can be briefly stated and readily visualized by the following statement of the sequence of events, viz. obstruction, stasis, infection, back-pressure. It is at once apparent, therefore, that a narrowing of the ureter constitutes a violation of a fundamental principle—the maintainence of free drainage. The deleterious effects which may be ascribed to this particular disturbance in function have been clearly and concisely set forth by Hunner in the following paragraph. "The more common renal diseases which in large measure may be traced back to the injury caused by ureteral stricture are hydronephrosis (sterile or infected), chronic pyelitis and pyonephrosis, pyelitis of the pregnant and puerperal periods, chronic pyelitis in children, renal and ureteral calculi, the renal inflammatory processes resulting in the so-called essential hematurias, and the various pathological processes which drive to the urologist the patient with congenital malformation of the upper tract. It is probable that many of the chronic nephritides resulting in multiple abortions are secondary to stricture, as are some of the chronic renal processes formerly considered as amenable only to medical methods of treatment."

The treatment of stricture comprises a diagnostic as well as a therapeutic phase. In the first premise the stricture is located and if passable its caliber determined, whilst in the second a therapeutic dilatation may be done. Urograms may or may not be made at this time depending upon the conditions encountered. It is important that visualization be done as early as practicable to the end that the type of stricture—single or multiple and the extent of ureteral wall involved—may be determined and information as to the condition of the renal pelvis be gained. In any case it is best to do one side at a time and not allow the patient to be ambulatory until the day following or until all pain has disappeared.

Ultimate success in the treatment of stricture per se depends upon the removal of foci of infection. The disposal of such areas eliminates further influence in the stricture zone and at the same time dispenses with possible deleterious effects in relation to other structures.

The number of dilatations in any given case will depend entirely upon the conditions encountered in that patient. As a rule the first two or three treatments, depending upon the temperament and reaction of the individual patient, should be received in the hospital while subsequent ones may be carried on in the urologist's office.

We have selected, from our series of about sixty cases, a few examples that will serve to illustrate some of the settings which have been dwelt upon in the text of this paper.

Case I. Mrs. T., age 46 years.

Family, menstrual, marital and past histories: negative.

Present complaints: Nervousness, ready fatigue, conscious irregularity of heart's action, breathlessness on exertion, intermittent annoyance and distress in epigastrium attended by pyrosis and gas after food, intermittent frequency.

Examination: Thyroid adenoma (moderately toxic), tachycardia (moderate), multiple extrasystoles, hypertension (moderate), physical evidences of gall bladder pathology, tenderness (sharp) in right kidney angle. Gastro-intestinal x-ray study negative. Radiography of gall bladder region revealed a constant solitary shadow.

Treatment outlined: a. ureteral catheterization; b. cholelithotomy, possible cholecystectomy with appendectomy; c. removal of thyroid adenoma.

Ureteral catheterization: Left normal. Right impassable at pelvic brim but bouginage succeeded after 3 or 4 trials with release of purulent colon-infected urine.

Diagnosis—urological: Stricture, hydropyonephrosis.

Treatment—urological: Dilatation at intervals with resulting relief of infection and restoration of practically normal kidney function.

Comment: The strictured ureter constituted symptomatically a seemingly minor part in this clinical picture. Relief of all other conditions and failure to have discovered this would have left this woman to face destruction of the right kidney with its train of evil consequences.

Case II. Mr. H. W. P., age 29 years.

Family, venereal and marital histories: negative.

Past history: Mumps, measles, a few sore throats, an average number of colds.

Present complaints: Four or five years ago a low grade, more or less constant "pressure pain" appeared in the right inguinal region; no complements, such as nausea or cramps are recalled. A chronic appendix was diagnosed and an appendectomy done; relief has not followed, on the contrary he is worse than before. Three third molars were removed two years ago without benefit. Gastro-intestinal studies and a cholecystography were done; the findings were said to disclose nothing distinctive, but questionable features in the history, led to the institution of an ulcer regime which was carried on for a year without improvement. During this period he had an attack of abdominal pain described as very severe and characterized by sudden onset; this was ascribed to too much laxative powder. At present—June, 1927—has an "old-fashioned stomach-ache" most of the time. There is more or less nausea and at intervals the abdomen is diffusely sensitive to touch. Attacks of generalized abdominal cramps followed by diarrhea of several days' duration occur not infrequently, the loose stools often contain much stringy mucus. Cramps frequently waken him in the morning. An abundance of gas with associated pyrosis and not related to the taking of food is common. Patient alleges that he has but little "pep" and less endurance; he may rest well at night, at times, and waken feeling well, but within a couple of hours be overtaken by a sensation of great fatigue. Under such conditions his color on rising has been observed to be good, but when the sense of exhaustion comes over him he will become pale and show dark circles under the eyes. He is nervous, irritable, easily annoyed and worried about his health and incidentally about his position because of lessening efficiency. There are no kidney-ureter-bladder tract symptoms.

Examination: Complexion muddy; fine tremor of extended hands; an intra-nasal contact interfering with drainage; a mild naso-pharyngitis; tonsils atrophic but show many retaining crypts, some of which are occluded; generalized abdominal tenderness with localized increase in the gall bladder area and on either side of and in close proximity to the umbilicus—no radiation noted;

sharp and well localized tenderness in both kidney angles; lower pole of right kidney felt on deep inspiration and slightly tender. Three urinalyses were done, one was entirely negative, the other two chemically negative, but the sediment in one showed a few pus cells and in the other an occasional pus clump.

Treatment outlined: Preliminary investigation of the K-U-B tract, further steps to be determined later; dietary regulation when all studies have been completed.

Ureteral catheterization: Bladder normal. No. 6 catheter obstructed at 4 cm. on right side; this was replaced by a No. 5 which passed the initial obstruction but was hindered in its further passage at 20 cm. On the left side a No. 6 passed readily into the pelvis. Differential function, appearance time of dye on right side 4 minutes, from left side 7½ minutes. Urograms were made.

Diagnosis—urological: Multiple strictures of the right ureter with a moderate hydronephrosis; probable stricture of the left ureter as visualized in urogram. No infection.

Treatment—urological: Dilatation of strictures at appropriate intervals, the latter to be determined by response.

Comment: This young man had passed through the hands of five or six of the outstanding physicians in this community and failing to get results had quite naturally become very skeptical. He submitted to the procedure outlined after due deliberation and when he was discharged from the hospital he stated to the Interne that he was free of pain for the first time in four years. Consent was given for a tonsillectomy but he demurred as to further x-ray studies, etc., alleging that he had had repeated observations of this sort without relief, but agreed that he would again submit if no improvement followed the ureteral catheterization.

September 27—'27. Three ureteral dilatations have been received and a tonsillectomy has been done. He reports that, aside from some trouble with increased intestinal gas following such foods as cabbage and cauliflower, he is well. He stresses the fact that his mind is more clear and that he is not nervous. Conscious heart's action of which he formerly complained has practically disappeared; his endurance has improved and he awakens refreshed in the mornings. Examination of the abdomen reveals much less tenderness and no suggestion of localization as previously mentioned. There has been a gain of 10 pounds in weight.

This patient is being seen at intervals and returns voluntarily for an occasional ureteral dilatation. His condition continues good and we can only conclude that the ureteral pathology has been in large part if not entirely responsible for his prolonged disability.

Case III. Mrs. A. M. P., age 40 years.

Family history: Negative.

Menstrual history: Periods always painful and very irregular, especially of late.

Marital history: Married at 17; divorced and history suggests that patient contracted a gonorrheal infection. Remarried; no pregnancies, no prevention practiced.

Past history: Rubella, parotitis, pertussis, diphtheria—a protracted ear complication followed the latter—, frequent colds, many attacks of tonsillitis.

A nervous complaining child, in fact has not changed to the present time. Stomach upsets and cramps frequent, usually ill two or three days each week.

Mild rheumatic joints for many years, relieved in great part by tonsillectomy.

Has had three laparotomies—an appendectomy, a partial oophorectomy, later—she was told—a total oophorectomy, but this was in error as she still menstruates.

Present complaints: Nervousness, irritability, despondency, frequent weeping often without provocation, easy fatigue, sleep not restful or refreshing, nocturia—2 or 3 times—headaches, often attended by nausea and vomiting—has vomited after each meal for

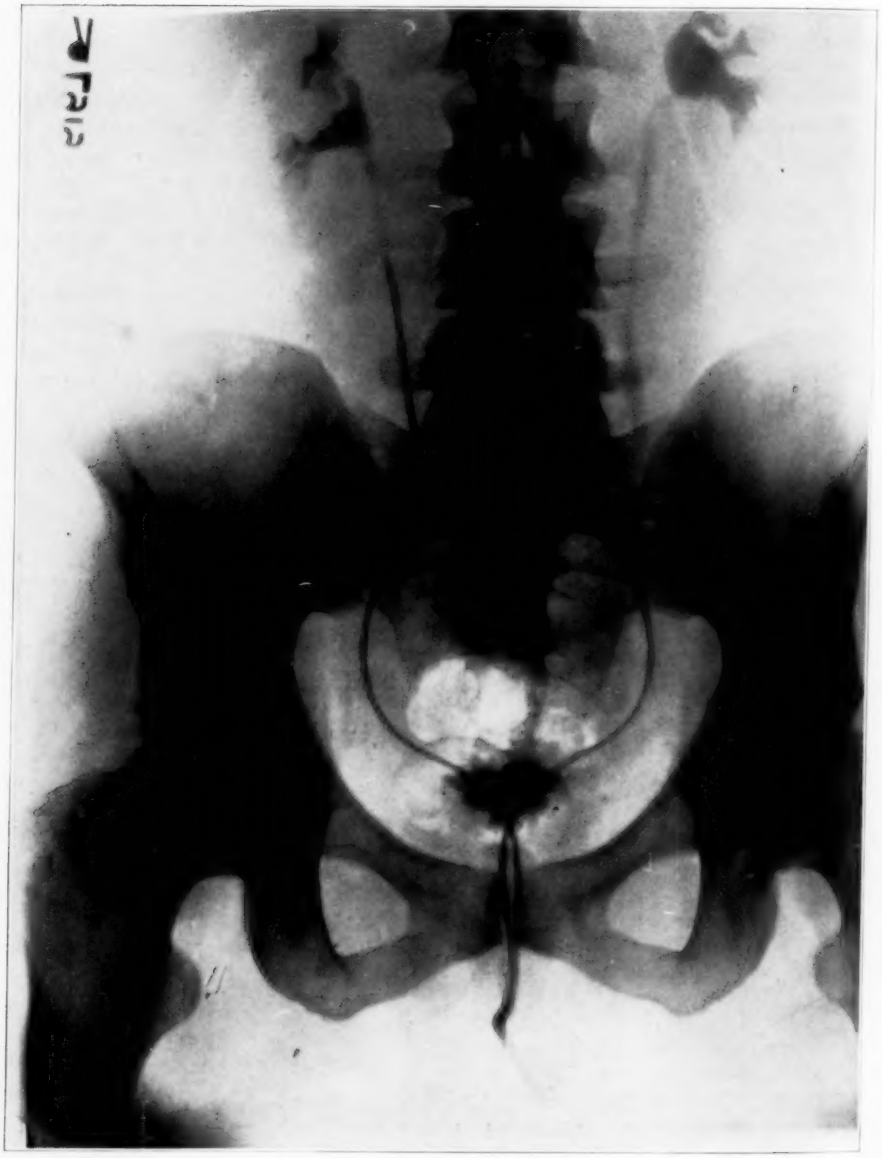

FIG. 1. Case 2. H. W. P. Bilateral Pyelograms. Stricture locations: Left ureteropelvic junction. Right upper ureter.

several days at a time—, much gas after food, frequent pyrosis, constipation, head pains in various locations and always made worse by excitement and disagreeable circumstances—pains are usually worse at night and in the early morning—, occasional precordial and frequent severe diffuse abdominal pains. Weight increased between the ages of 25 and 30 and has not declined despite the disturbances cited.

Examination: A healthy appearing, somewhat overnourished woman; weight 158 pounds; height 5′5″; three devitalized teeth —radiographically negative—, mammae very sensitive to touch; gall bladder reacts sharply to all physical manoeuvers; moderate diffuse abdominal tenderness—sharp localization about laparotomy scar, not possible to establish relationship of tenderness to any definite underlying structure—; tenderness in both kidney angles; sharp tenderness over upper end of right sacro-iliac joint; remaining pelvic structures normally posed; marked diffuse bi-manual tenderness.

Catheterized urine showed albumin a slight trace, leucocytes and a few pus clumps, a few calcium oxalate crystals.

Treatment outlined: Investigation of K-U-B tract first. Subsequent course to be worked out pending the results of this study.

Ureteral catheterization: Bladder mucosa paler than normal; ureteral orifices within range of normal. A No. 5 catheter obstructed 7 cm. above right orifice but finally passed to pelvis of kidney; abundant clear urine drained and following this 12 c.c. were withdrawn by light suction. On the left side a No. 5 catheter passed readily to the kidney; urine clear. Differential function, left kidney appearance time 2½ minutes, right 6 minutes. Urograms were made. Patient complained bitterly of pain at about the level of the obstruction in the right ureter when the iodide solution was being injected.

Diagnosis—urological: Stricture, first degree hydronephrosis, infection and slight nephroptosis on right side.

Treatment—urological: Dilatation of stricture at suitable intervals with treatment of the infection.

Comment: This case appeared like a hopeless situation and an attitude of skepticism toward the procedures suggested was evident. Such an attitude has been engendered by years of disappointing medical and surgical treatment. Several months have elapsed and the patient has returned for treatment on four or five occasions; she has been carefully observed and attention given to devitalized teeth, the dietary, etc. She is taking no medicine and alleges that in the main she is well. The husband states without reservation that his wife has not been as well in years. In the beginning we entertained a reasonable doubt as to the reliability of the patient's glowing reports of relief, but at this time there is seemingly ample proof that the glamor of the initial benefit was real.

Case IV. Miss A. G., age 24 years.

Family history: Father died of brain tumor at age 57; otherwise negative.

Menstrual history: Periods always regular but painful, especially so in the past few months. Latterly all complaints are aggravated at the menstrual times and she shows a disposition to become hysterical.

Past history: Rubella, varicella, parotitis, scarlet fever—all without known sequelae. Frequent tonsillitis until tonsillectomy at age 19. A healthy child. In early adolescence began to be nervous; sick headaches (not menstrual) appeared, but have lessened in frequency in later years; began having nervous spells characterized by periods of exhaustion; a digestive disturbance of intermittent manifestation and apparently unrelated to the taking of food gradually developed and continues to the present time—has pyrosis, gas after food, occasional generalized abdominal cramps; soda occasionally relieves—. Patient does not smoke or use liquor.

Present complaints: Very nervous all of the time, irritable, restless, lack of endurance, inability to concentrate on her work because of periods of mental vagueness, noc-

turia—about 3 times—appeared about the same time as the digestive disturbance and like it is subject to remission, very sensitive to cold.

Examination: A rather frail young woman with an expression suggesting depression. Weight—net—115 pounds; height 5′8″—estimated. Complexion muddy; rather coarse but fairly rapid tremor of the extended hands; tongue tremulous and heavily coated; gall bladder reacts slightly to physical manoeuvers; cecum partially filled and can be rolled under the finger; fairly well localized but moderate tenderness in vicinity of McBurney's point, also in the median line about 1½ inches below the umbilicus with radiation upward in the median line; well localized tenderness in the right kidney angle; pelvic negative.

Fractional gastric analysis disclosed a moderate hypoacidity. Gastro-intestinal study negative excepting a retention of barium in the appendix with tenderness on manipulation. The blood showed a moderate reduction in hemoglobin and total red count. Basal metabolic rate estimation gave a —2%. Catheterized urine showed a few leucocytes in the sediment only.

Treatment outlined: Preliminary investigation of the K-U-B tract; possible appendectomy later; dietary regulation.

Ureteral catheterization: Bladder mucosa pale. A No. 6 catheter was obstructed in its passage at 20 cm. above the bladder and was replaced by a No. 5 which passed the narrowed area with difficulty. Another obstruction was met at the uretero-pelvic junction which was also passed with difficulty. On the left side a No. 6 passed readily to the kidney. Differential function, the appearance time on the right side was 12 minutes, on the left side 3 minutes. Urograms were made.

Diagnosis—urological: Double stricture of the right ureter. The one at the ureteropelvic junction of the pipette type.

Treatment—urological: Dilatation of strictures at intervals.

Comment: This patient has been examined in Europe and for the past three years has been under the care of the Staff in a large closed hospital. The only treatment prescribed in the latter institution was 2 grains of thyroid extract daily; the discontinuance of this lessened the nervousness definitely. An examination by a psychiatrist in Boston resulted in her being classified as a non-reader. Our study of the case led to the following beliefs: a. a possible slight thyroid hypofunction; b. ovarian dysfunction; c. a digestive disturbance of extra-gastric origin; d. moderate intestinal stasis; e. possible pathology along the kidney-ureter-bladder tract. The peculiar mental reaction could not be based upon any evident findings. The first ureteral catheterization was received in September and following this she returned to her studies in an eastern college. Reports were received that the quality of her work had improved, the digestive disturbance had been in abeyance, the nocturia had not returned, sleep was more refreshing and there was less nervousness. During the Christmas holidays she returned for further treatment. At this interview the patient added to the above that dizziness which formerly troubled her considerably had disappeared, the vague periods (mental) seemed less definite and that she is not quite so tired as has been her habit to be. An examination of the abdomen disclosed a total absence of all areas of tenderness.

We believe that the discovery of the strictures on this case was very timely and that the treatment given has had much to do with the improvement in her health. It is also our belief and hope that she will experience further benefits in the future.

Four other case protocols are included in this communication but are reported in less detail than the first four.

Case V. Mrs. E. R., age 35 years.

Family, menstrual, marital and past histories: negative.

Present complaints: Headaches, loss of weight, general weakness, constipation, frequency, pain in right kidney area, inability

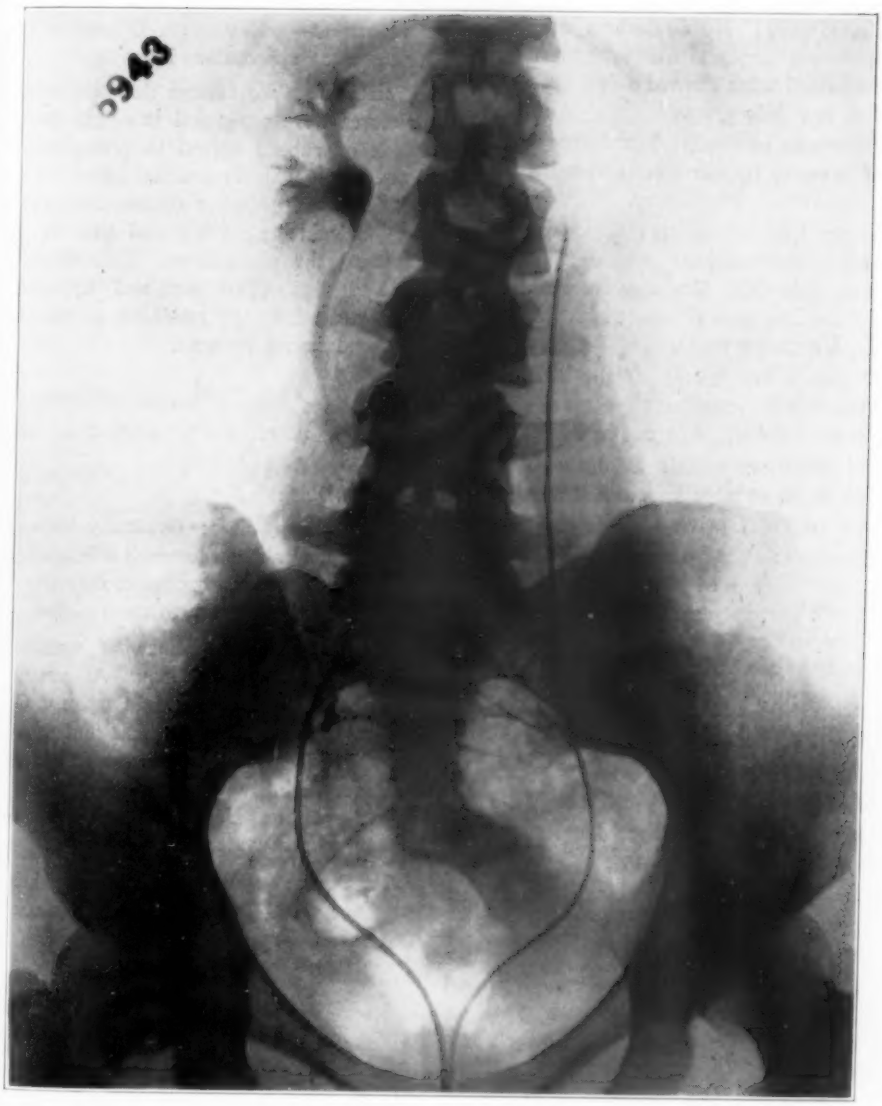

FIG. 2. Case 4. Miss A. G. Right Pyeloureterogram. Stricture (pipette) at right ureteropelvic junction.

to carry on household duties because of lack of strength. Has received prolonged treatment directed toward the gastro-intestinal tract without notable benefit.

Examination: No disclosures were made that would explain the symptomatology. Catheterized urine showed a few pus clumps and a few leucocytes.

Treatment outlined: Initial study of the K-U-B tract; further investigations to await the outcome of this inquiry.

Ureteral catheterization: Bladder normal. Catheter obstructed at uretero-pelvic junction on right side. Drainage from right kidney scant and function decreased. Left normal. Urograms made.

Diagnosis urological: Tight stricture at uretero-pelvic junction; moderate hydronephrosis; definite loss of function.

Treatment urological: Dilatation of stricture zone at suitable intervals, drainage and lavage of renal pelvis.

Comment: This patient has been almost entirely relieved of the general symptoms of which she complained and experiences no further urinary tract annoyance. Dietary regulation is observed but no medicine is being taken.

Case VI. Baby G., age 3 years

Family history: negative

Past history: negative excepting an attack of measles nine months ago.

Present complaints: Weakness, anorexia, pallor, pain in the lower abdomen. All symptoms appeared following the attack of measles.

Examination: No noteworthy physical findings excepting an apparent loss of weight and diffuse tenderness over the lower abdomen. Blood Wassermann negative. Blood count showed a moderate secondary anemia. Preliminary urinalyses negative but later studies disclosed a few leucocytes only.

Treatment outlined: Cystoscopy, probable catheterization of the ureters; later procedures to be developed following this study.

Ureteral catheterization: A mild cystitis. Right ureter obstructed 9 cm. above the bladder and the left 7 cm. above the bladder. Urograms were made.

Diagnosis—urological: Bilateral multiple strictures, hydroureter and hydronephrosis.

Treatment—urological: Dilatation of strictures at appropriate intervals.

Comment: We believe that the ureteral strictures were congenital in origin and the attack of rubella served to precipitate the symptoms. The immediate effect of the measles virus or other concomitant irritant was undoubtedly edema and this in turn increased the obstruction. This child has received two dilatations and appropriate tonic treatment; his condition is markedly improved in all respects.

Case VII. Mr. T. M., age 58 years.

Family, venereal and marital histories: negative.

Past history: Negative.

Present complaints: Gradually increasing frequency, weakness, lessened efficiency, loss of weight, anorexia, backache, digestive disturbance with tendency to constipation.

Examination: A somewhat undernourished tired-appearing man. A group of semipersistent râles in right apex. Colon moderately distended with gas and more or less sensitive over its course. Tenderness in the right kidney angle. A moderately enlarged prostate. Urinalysis disclosed a trace of albumin, a moderate pyuria.

Treatment outlined: Preliminary investigation of K-U-B tract. Other measures to be held in abeyance until this study has been completed.

Ureteral catheterization: Right ureter normal. The left ureter narrowed to small caliber at 7 cm. above the bladder and again at the uretero-pelvic junction. Urograms were made. Complete loss of function on the left side according to the dye test.

Diagnosis urological: Cystitis: enlarged prostate; residual urine, infected—amount 250 cc.; double stricture of left ureter with associated hydronephrosis (capacity of renal pelvis exceeds 6 cc.).

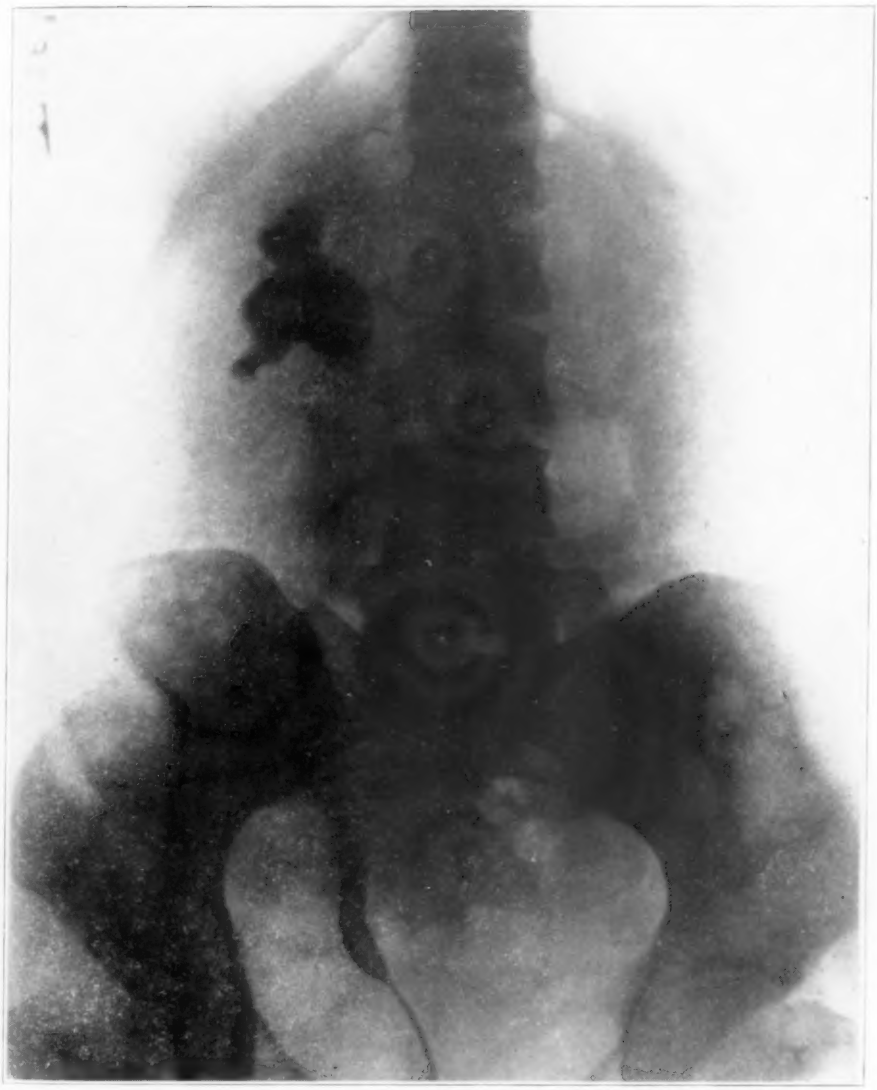

FIG. 3. Case 5. Mrs. E. R. Right pyelogram, and partial ureterogram. Suggests stricture at ureteropelvic junction and in lower ureter segment (catheter passed into ureter and turned upon itself, failing to pass lower stricture).

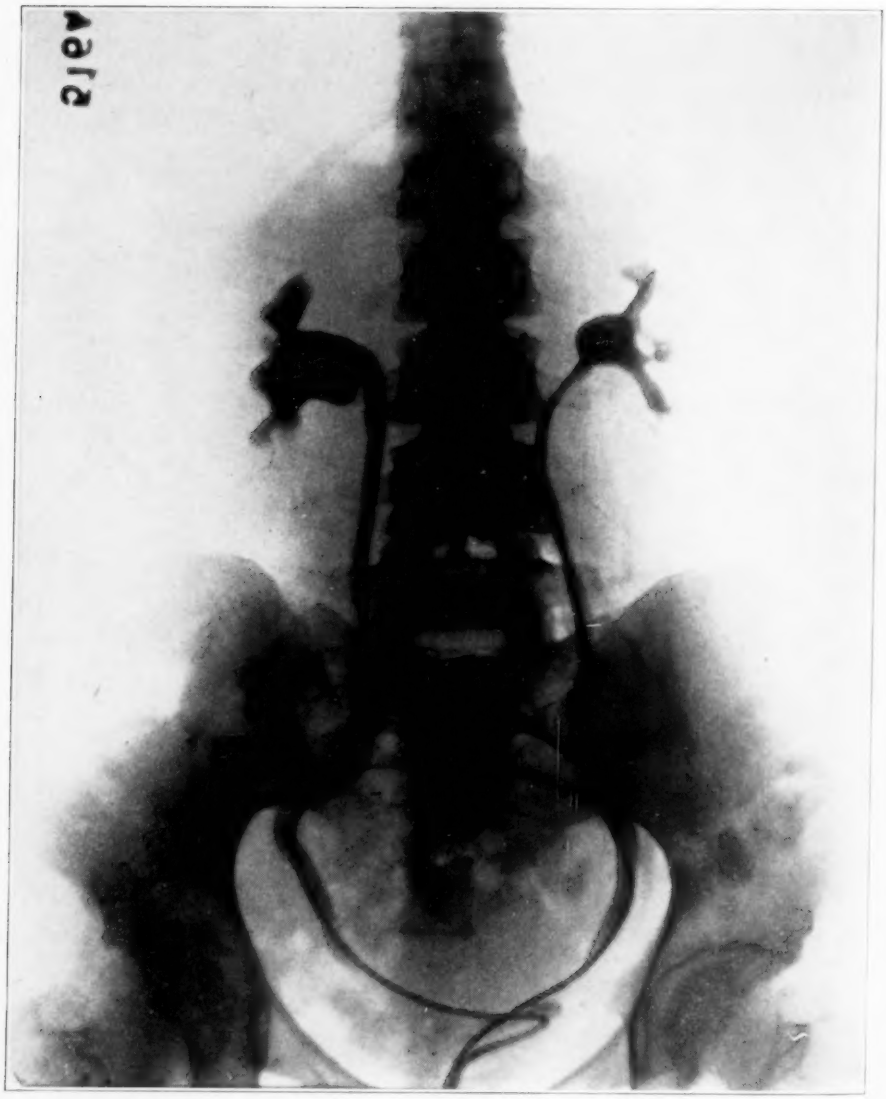

FIG. 4. Case 5. Mrs. E. R. Bilateral pyelograms. Stricture at ureteropelvic junction, both sides, with high insertion of ureter, on right side. Compare with Fig. 3, and note lessening of hydronephrosis. This study made after relief of symptoms.

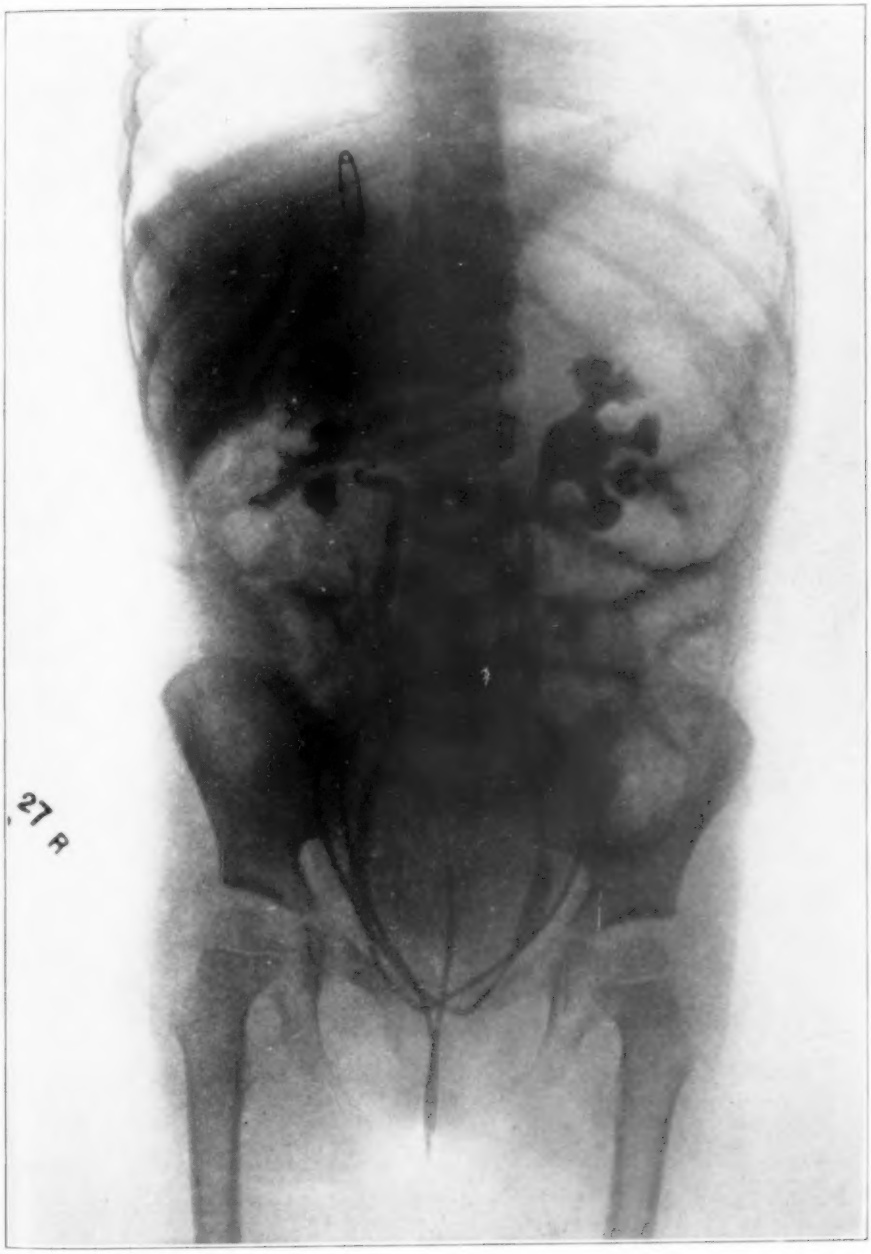

FIG. 5. Case 6. Baby G. Bilateral pyeloureterograms. Note pyelectasis and kinks and dilatations of ureters. Bilateral strictures of midureters. See text.

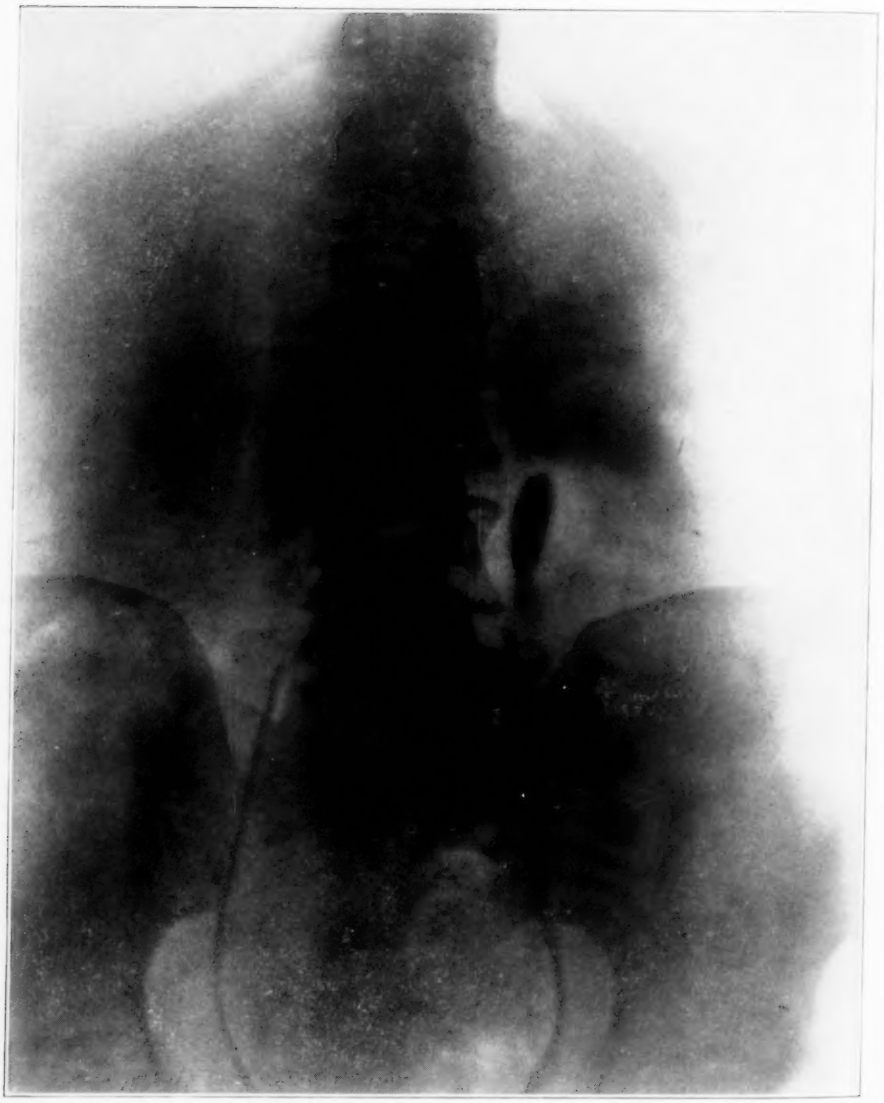

FIG. 6. Case 7. Mr. T. M. Left pyelogram. Marked hydronephrosis and two stricture areas, one near pelvis and one in m.dportion of ureter. See text for notes on case.

Treatment urological: Appropriate treatment of cystitis; dilatation of strictured ureter with drainage and lavage of the renal pelvis at 30 to 90 day intervals; urinary antiseptics internally.

Comment: This patient has been under treatment for about one year. He has gained in weight and has been relieved of his backache since the first treatment. The left ureter is patent, the bladder function and the urine are normal. There has been an entire absence of symptoms for more than six months. The pulmonary condition has cleared—a relationship between the pulmonary findings and the infection along the urinary tract is not alleged but it is known that in generalized tuberculosis an active process along the intestinal or urinary tracts will keep a pulmonary lesion from becoming quiescent. No other treatment than that given with dietary regulation has been received. A former diagnosis of colitis, cystitis and possible pulmonary tuberculosis had been made.

Case VIII. Miss J. S., age 14 years.

Family and menstrual histories: Negative excepting as noted below.

Past history: Frequent attacks of tonsillitis. Tonsillectomy has been done.

Present complaints: Recurring attacks of pain in left flank, often accentuated during menstruation.

Examination: Well nourished but pasty looking girl. Physical examination otherwise negative excepting a slightly palpable and very tender left kidney. Tenderness in kidney angle sharp. Urinalysis: a trace of albumin, a few hyaline casts, an occasional leucocyte and erythrocyte.

Treatment outlined: Catheterization of left ureter.

Ureteral catheterization: Slight cystitis. Obstruction of left ureter at uretero-pelvic junction; following passage of impediment cloudy infected urine drained. Right side normal.

Diagnosis—urological: Stricture at uretero-pelvic junction with moderate hydronephrosis.

Treatment—urological: Dilatation of stricture at appropriate intervals.

Comment: The symptoms have been entirely relieved and the urine has returned to normal. This patient continues in apparent full health at the end of one year.

Summary

Eight cases have been reviewed. The results thus far justify reasonable enthusiasm but it must not be understood that the study has become a fetish and a hope established that a therapeutic path to Elysian fields has been discovered. On the contrary we have established, from our own studies as well as those of others, a firm conviction that there are a large number of people who are victims of this condition to whom benefit, such as has been described, might accrue if obscure situations with only suggestive symptoms could be intelligently and painstakingly investigated.

Our interest in this condition was very modestly aroused several years ago but not until the past year did we take up the study more intensively. Thus far we have collected sixty-two cases most of which have been brought to light in the latter period. In this group there have been many striking examples of sustained benefit, some who have reported improvement in some respects only and others in whom we have been frankly disappointed.

In this series there are 18 males and 44 females: the age variation has been from 3 years to 61 years: the largest number of cases was in the fourth and fifth decades. There were 31 patients with symptoms referable to the genito-urinary tract and 31 whose complaints bore no relation

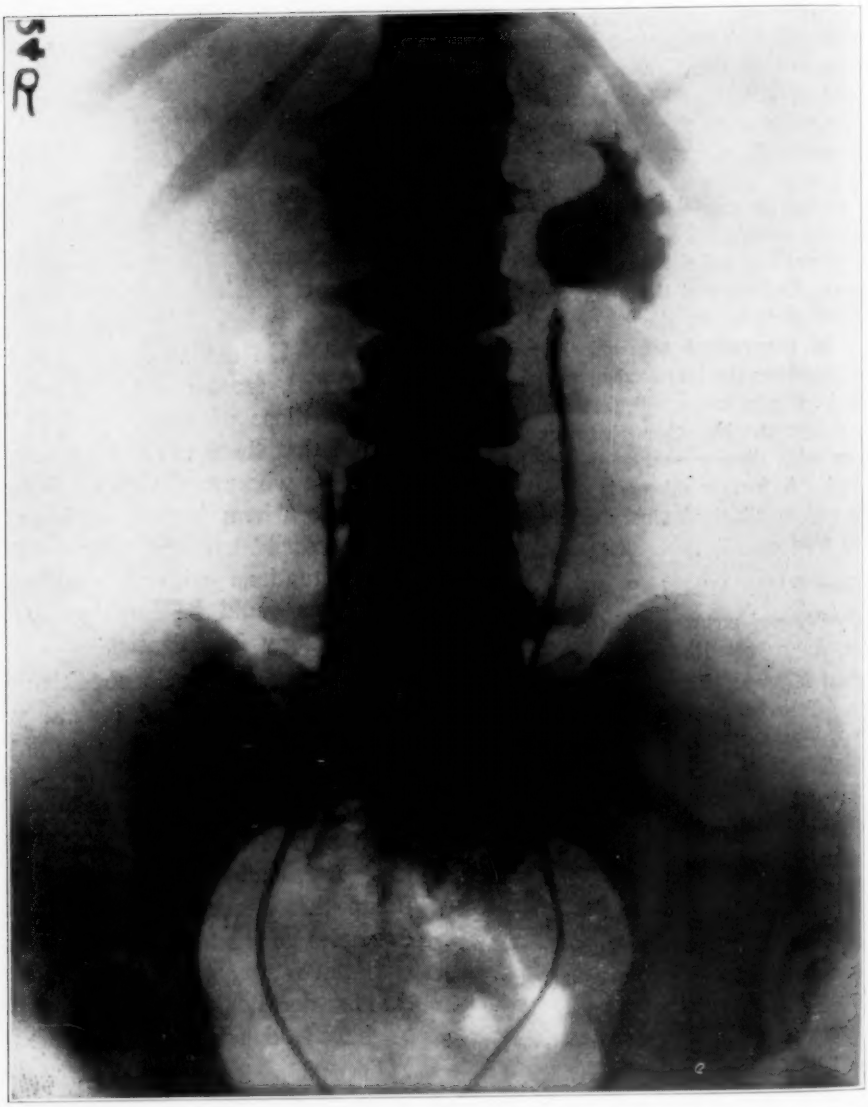

FIG. 7. Case 8. Miss J. S. Left pyeloureterogram. Stricture at ureteropelvic junction, pyelectasis. See text.

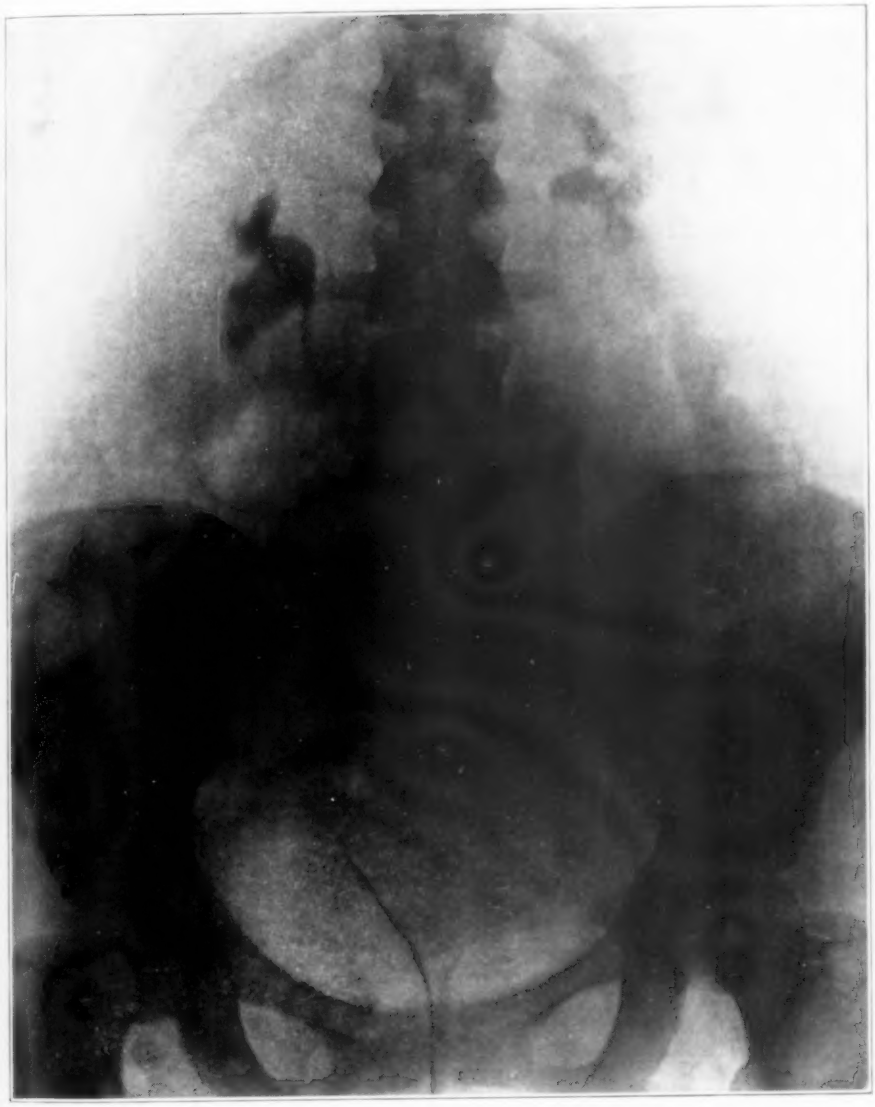

FIG. 8. Case 49. Miss W. Bilateral pyeloureterograms. Multiple strictures both ureters; more accurate demonstration made by bouginage. Also slight right hydronephrosis. This patient had a series of antecedent infectious diseases and chronic tonsillitis.

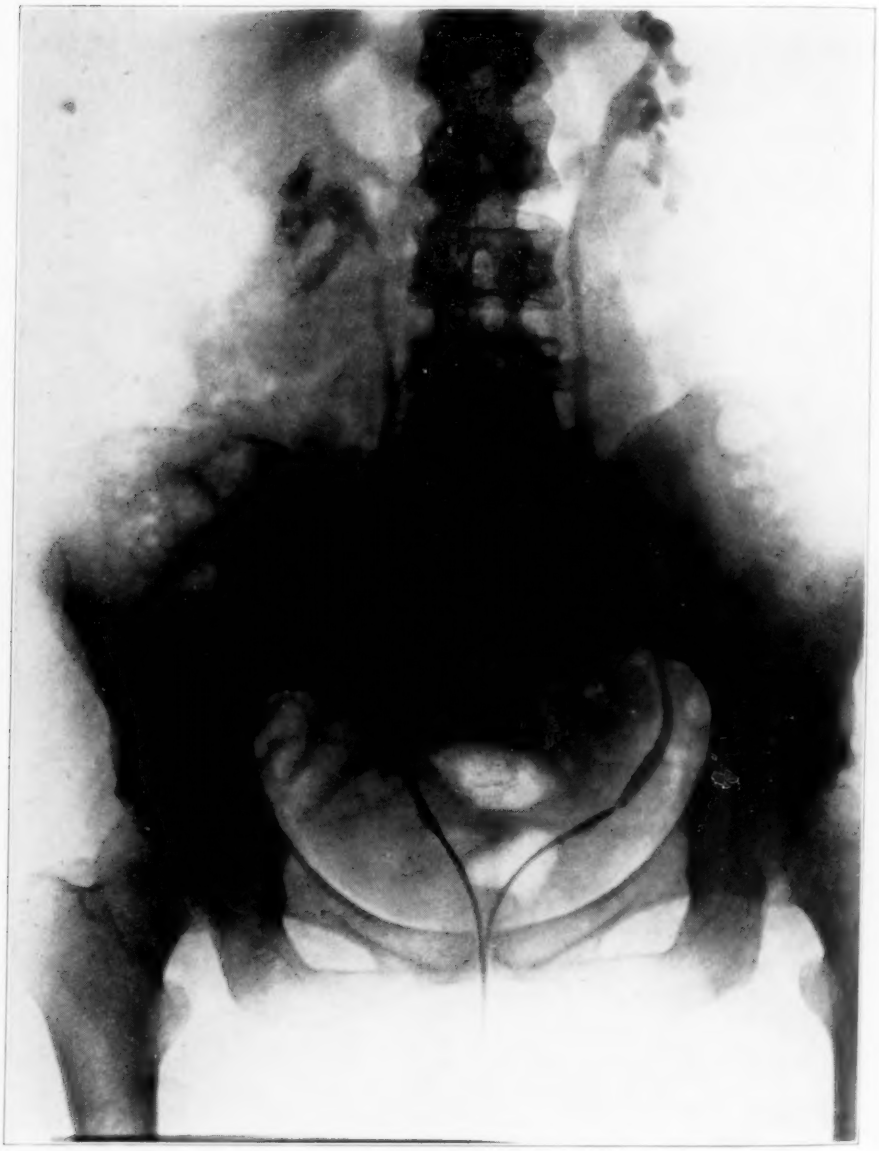

FIG. 9. Case 53. Bilateral pyeloureterograms. Multiple irregularities of ureters proven strictures by careful instrumentation.

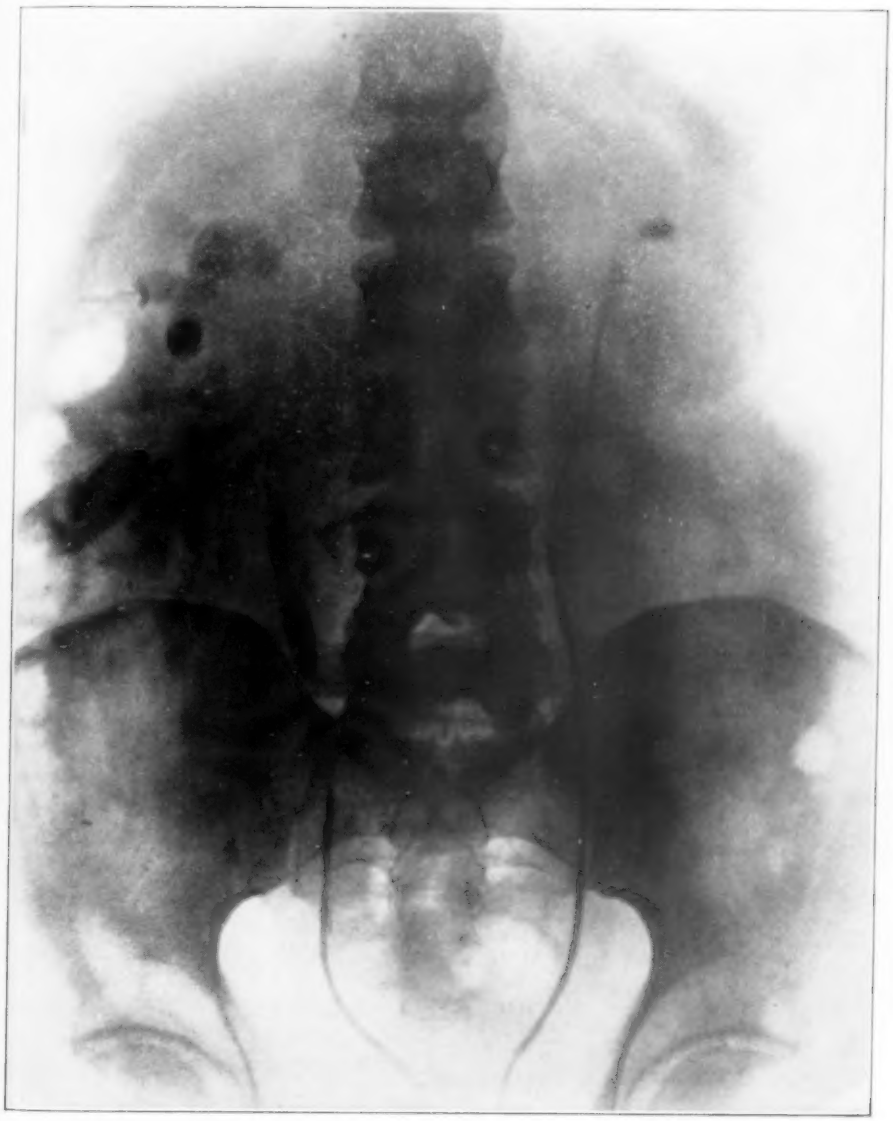

FIG. 10. Case 33. Mr. D. G. Bilateral pyeloureterograms, demonstrating strictured areas in upper ureteral segments; both associated with pyelotomy for stone. Following operation on left side kidney has atrophied and is functionless; only a small part of pelvis remains.

to such involvement. Thirty-nine cases showed unilateral stricture and 23 bilateral pathology.

Conclusions

1. We believe that ureteral stricture is of very frequent occurrence and that it represents a definite clinical entity.

2. The recognition of symptoms suggestive of ureteral pathology does not require special training.

3. We believe that patients in whom a diagnosis of chronic appendicitis seems logical but unsupported by a history of attacks as well as patients with chronic gall bladder manifestations—with or without stone—should receive an investigation of the kidney-ureter-bladder tract before surgical procedures are instituted.

4. No patient with recurrent urinary tract symptoms should be treated symptomatically alone and surgery should not be resorted to as a diagnostic procedure until after an investigation has proved with reasonable satisfaction that the ureter is not at fault.

5. Collaboration of the medical man and urologist is of great importance to the end that more cases may be brought to light.

6. The non-surgical nature of ureteral catheterization commends it as a diagnostic procedure.

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Management of the Goiter Patient*

By Willard C. Stoner, M.D. *Cleveland, Ohio*

PRESENT day observation indicates that thyroid disease is more prevalent than formerly and this is especially true of the adolescent goiter. Notwithstanding a vast amount of investigative work in the problem of thyroid disease the true cause remains more or less speculative. However, there are certain essential factors that have a definite bearing on the disease, the most outstanding of which is the one evolved by Marine and Lenhart, in which they have shown rather definitely that it is in part at least an iodine deficiency disease. The literature on thyroid disease is voluminous and much attention has been given the various phases of hyperthyroidism, particularly from the standpoint of surgical treatment. More recently attention is being focused on the prophylaxis of simple goiter. It is obvious that from an economic standpoint prophylaxis is extremely important.

Municipal and State governments have taken up a consideration of the problem from the standpoint of control. As far back as 1864 France appointed a commission for the study and relief of endemic goiter. At that time the commission reported 500,000 goitrous people and 120,000 cretins. Early in the sixteenth century Paracelsus emphasized the relation between endemic goiter and cretinism. Goiter as a disease has been traced back to 2,000 B.C. It was in 1825 that Parry described the goiter syndrome and Graves in 1835 gave an accurate description of exophthalmic goiter. Basedow in 1840 published a monograph on the same disease. Sir Wm. Gull in 1874 described a clinical complex which represented myxedema and associated it with thyroid deficiency. Kocher in 1883 reported myxedematous states following removal of goitrous thyroids. A little later Horsley produced experimental myxedema in monkeys. In 1891 Murray and MacKenzie administered thyroid extract to myxedematous patients and obtained clinical results. A little later these observations were confirmed by Magnus Levy. Baumann discovered in 1891 that iodine was the normal constituent of the thyroid gland and in 1901 Marine showed that iodine was necessary to normal thyroid function and if sufficent iodine is present in the system, an active hyperplasia of the gland does not occur. Thyroxin as an iodine-containing hormone of the gland was isolated by Kendall in 1915. Observa-

*Presented before the American College of Physicians at St. Luke's Hospital, Cleveland, Ohio, February, 1927.

tion has shown that diffuse colloid and adenomatous types of colloid goiters can be prevented by the proper administration of iodine. This fact together with the fact that goiter occurs commonly where water and soil are poor in iodine, makes iodine deficiency the probable exciting cause of adolescent goiter.

The theory has been advanced that bacterial flora in the intestinal tract prevent the utilization of available iodine. This theory has been advanced as favoring the bacterial origin of goiter. It is known that the physiological activity of thyroid extracts is in proportion to the iodine content. It is known that goitrous districts are distant from the seashore and that the water supply is very largely free from iodine. Experimentally it has been shown that polluted water produces goitrous changes in fish. McGarrison champions the bacterial infections cause contending that the colon group which are water borne are responsible; that the gastro-intestinal tract infection interferes with the normal absorption and assimilation of iodine. Systemic or focal infections may produce a reaction in the thyroid resulting in thyroid toxicity, e.g. the exophthalmic type of toxic goiter. The occurrence of adolescent goiter incident to puberty and the preponderance in the female is estimated by ratios varying from 4 to 1 to 10 to 1. This preponderance in the female is responsible for the thyroid being designated as an accessory ovary. It has been known for centuries that there is an intimate relation between the thyroid gland and menstruation, that the gland enlarges just previous to the flow. May not the stress of modern life tend to encourage thyroid disease? May it not be true that the body economy may fail to adjust itself fully to the demands of modern life and as a result increased metabolism calls for increased iodine which results in increased gland activity; therefore an increase of thyroid disease. It has been known for a long time that thyrotoxicosis in varying degrees occurs incident to stress and worry in life.

The goiter of adolescence produces few or no symptoms and is represented by a smooth, soft, uniformly enlarged gland. The exceptional case may develop symptoms in the way of increased fatigue, irritability, nervousness, tachycardia, weight loss, sallowness and constipation. This case generally represents the one whose adenoma has been present for a period of time, who is living speedily or who possibly is the victim of faulty iodine therapy. Such a condition may rapidly develop into a true toxic goiter. It is this type of case where basal metabolic rate observations are of differential value. The adolescent goiter patient with nervous symptoms unassociated with the goiter will not maintain a basal metabolic rate above normal when placed at rest in bed for a period of time. This is in contradistinction to the true toxic goiter syndrome. The goiter of adolescence untreated more often undergoes a spontaneous cure. The exceptional case may develop cystic, colloid or adenomatous degeneration which later may result in toxic goiter or give mechanical

disturbance by pressure on adjacent structures.

Common signs of hyperthyroidism are (1) cardiovascular reactions that represent an increased minute flow of blood from the heart; (2) increased hypertension, sweating and elevation of surface temperature, increased heart rate; (3) increased caloric intake to maintain body weight; (4) a group of nervous symptoms resulting from irritation stimulation and fatigue of the nervous system resulting in visceral and tissue degeneration.

The symptoms of exophthalmic goiter are those of hyperthyroidism accentuated plus exophthalmos. The cause of exophthalmic goiter is not known. It represents a stimulation from some unknown source on the entire thyroid gland producing an agent probably abnormal in quality and in quantity, which in the tissues of the body cause all the phenomena of the disease. Exophthalmic goiter develops abruptly in contradistinction to hyperthyroidism which develops insidiously and occurs more commonly in an earlier period of life than hyperthyroidism. The basal metabolic rate in exophthalmic goiter averages much higher than in hyperthyroidism. It is interesting to note that a large per cent of exophthalmic patients have an enlarged persistent thymus. Cardiac disturbances are more marked in exophthalmic goiter than in hyperthyroidism. Auricular fibrillation is relatively common. The clinical course of exophthalmic goiter is variable. The milder case goes on to spontaneous cure but the severe case succumbs to the disease if not relieved by medical or surgical management. It is important to operate the exophthalmic case early before irreparable damage is done to the heart musculature and other viscera. The exceptional case will respond to medical management.

There is a diversity of opinion even now as to what shall constitute the management of the goiter patient. More careful clinical study together with metabolic rate observations no longer leaves the diagnosis uncertain in a large per cent of the toxic goiter cases. Surgical treatment of toxic goiter was introduced empirically and in spite of much scientific knowledge which has been developed about the disease complex, it still remains popular as satisfactory treatment in a large per cent of the cases for the reason that no other form of treatment has so routinely given satisfactory results. Whatever more than a dysfunction of the thyroid gland characterizes the picture known as toxic goiter, the fact is established that removal of a gross portion of this dysfunctioning gland results in an interruption of the symptoms which characterize the disease. If removal of sympathetic ganglia for angina pectoris (it matters not what may be responsible for the symptoms of angina pectoris) had resulted in satisfactory clinical improvement no doubt the operation would have been popularized as goiter surgery has been popularized. Toxic goiter, whether toxic adenoma or Graves' disease is primarily a medical disease and should have primary medical management. The value of absolute bed rest plus the judicious use of iodine therapy in the form of Lugol's solution should be

taken advantage of in the routine management of every case of hyperthyroidism and bed rest must mean rest away from home environment always. It is absolutely impossible to manage satisfactorily the toxic goiter patient in the home. Such a period of management has three purposes, first to confirm a diagnosis; second to prepare for surgery if surgery is advisable and third to determine the case that will satisfactorily respond to medical management. If such management is practiced as a routine, the psychoneurotic, the neurasthenic and the nervously unstable with the irritable heart will not be subjected to needless and harmful surgery. I have been surprised myself how frequently I have found surgery not to be necessary after such a period of management where earlier observation was misleading not only diagnostically but therapeutically. If surgery is applied routinely early without careful diagnostic discrimination surgery will be abused. If preliminary management is not practiced as a routine you will have no satisfactory means of absolutely determining the border line ase or ruling out the psychoneurotic with a colloid goiter. This puts goiter surgery on the same plane with the appendectomy—Deaver's dictum, "better to take out a normal appendix than to leave in a diseased one." There are those who argue that goiter surgery is not scientifically sound, that no satisfactory explanation has been made of the rationale of the procedure and therefore it is to be condemned. Until medicine has found a satisfactory cure for a much larger per cent of the cases of toxic goiter than is true today I shall be rather liberal with the surgeon's lack of satisfactory explantaion of the cure of the disease but be guided by the results that have been so satisfactory in so large a per cent of cases subjected to goiter surgery. In a recent visit to European clinics I was greatly surprised to learn that they believe in certain clinics that the treatment of goiter is largely medical. I could excuse them on the ground that they see comparatively little goiter and therefore their experiences have not gotten them into the proper channel. X-Ray and radium as a means of treating goiter have not gained popularity generally; our results have been disappointing and I am of the opinion that radium therapy has very limited value in the treatment of toxic goiter. Lugol's solution in ten, twenty or thirty drop doses t.i.d. has been helpful in lessening toxic symptoms in all cases either exophthalmic or toxic adenoma. Frequent basal metabolic rate determinations have been valuable in checking clinical improvements as well as helpful in determining diagnosis. I think results of metabolic tests should be carefully checked as there is great liability to error if technique and conditions are not carefully controlled. I do not think slight elevations in basal rates should be given weight independent of clinical signs. We hear much of the abuse of iodine administration either as contained in iodized salt or other forms of administration. I think much of this criticism is overdrawn and conclusions are gotten without facts to prove. The tremendous value of iodine administered in proper quantities as a preventive of goiter has been

accepted. Because a few isolated cases develop toxic goiter who have taken iodine or iodized salt as a preventive should not answer as an argument against the judicious use of iodine. I would rather believe that the quantity of iodine was too small to be of value in isolated cases. It will take careful observation to prove that the judicious use of iodine as a preventive is objectionable. Of course the injudicious use of iodine in any form is to be condemned. The insidious development of toxic goiter with gastro-intestinal symptoms is not always easy of diagnosis. The high basal rate in this type of case is very satisfactory confirmatory evidence. Goiter hearts lead to diagnostic confusion, this is particularly true of disturbed mechanisms such as auricular fibrillation. Control of fibrillation and re-establishment of compensation clear the confusion. Most cases of fibrillation will respond to intensive digitalis therapy and I prefer intravenous digitalis therapy. The occasional case that is not controlled with digitalis will be controlled with quinidine in 2/10 gram doses q 4 or 6 h. If fibrillation is not controlled surgical interference is advisable in spite of fibrillation. A fibrillating heart that fails to respond to therapy before surgery will often respond after surgery. The case that encourages you to apply medical management is the one that shows a definite improvement after a period of two or three weeks at rest in bed with iodine therapy, in which there is a distinct lessening of tachycardia, tremor, increase in weight and a definite drop in the basal metabolic rate. Graves' disease developing incidental to diabetes is controlled with diabetic management where insulin therapy is taken advantage of. Mrs. G. age 58 yrs., a severe diabetic, managed in 1920-21, developed acute marked signs of Graves' disease early in 1922. She was managed with difficulty over a period of months and suffered marked weight loss. Late in 1922 insulin became available and was administered continuously in varying quantities for a period of six months during which time the symptoms of Graves' disease largely disappeared, the metabolic rate approached normal, there was a weight increase from 111 lbs. to 138 lbs., there was a marked drop in cardio-vascular hypertension which had ranged from 160/90 to 190/100, and a distinct improvement of carbohydrate tolerance. She was under observation throughout 1924-25 during which time her carbohydrate tolerance remained relatively good and the symptoms of Graves' disease had completely subsided. This recovery took place without apparent visceral damage and it would seem that insulin as an internal secretion played some part in the amelioration of the symptoms of Graves' disease.

In a series of 83 cases of thyrotoxicosis managed in the last few years, 32 were subjected to medical and surgical management and 51 to medical management alone. Eight cases of Graves' disease had bed rest, iodine therapy and high caloric feeding an average of 25 days before surgery. There were 5 males, 3 females and the average age was 41 yrs.; the average metabolic rate was plus 66 and the average metabolic rate after surgery

was plus 27. There were no deaths in our clinic and complete restoration to work was obtained in all cases. One patient, a male, age 36 yrs. showed very decided improvement under medical management but on account of his work being that of a detective it seemed advisable to have surgery rather than subject him to the possible uncertainty of final medical cure. He was apparently a good surgical risk and was operated in another clinic but for some unaccountable reason developed a severe hemorrhage and died twelve hours after surgery; but this was not a goiter death. Twenty-four cases of toxic adenomas were subjected to surgery after an average period of medical management of 3 months, 17 days. There were 5 males and 19 females, the average age was 39 yrs., the average metabolic rate before surgery was plus 57 and after surgery plus 16. Five cases of exophthalmic goiter were subjected to medical management alone—2 males and 3 females; average age 43 yrs., average metabolic rate before management was plus 21. There were seven- plus 16. These cases were kept under observation over an extended period and have been restored to full working efficiency. Forty-six cases of toxic adenoma were managed medically, 9 males and 37 females, average age 41 yrs., average basal rate before management was plus 47, after management was plus 21. There were seventeen cases classified as hypothyroid, 2 males and 15 females in which the basal metabolic rate varied from minus 5 to minus 29 with an average of minus 7, one of which was a marked case of toxic adenoma with a maximum basal rate of plus 44 and became a hypothyroid on medical management with a basal rate of minus 29. The other was a marked exophthalmic case with a maximum basal rate of plus 45, who developed signs of myxedema with a basal rate of minus 23 two months subsequent to surgery. Three of these cases were definitely myxedematous. All responded to thyroid therapy.

It remains to be seen what the eventual outcome of the toxic goiter case will be that responds to medical management. At most medical management must be regarded as an arrest of the disease activity but not always an absolute cure. A number of these cases were managed medically for the reason that they refused to have surgery. It is gratifying to report that not a single fatality in our clinic has occurred in the last five years in the toxic goiter cases managed either medically or surgically. Team work in the goiter problem is highly important. The condition is both medical and surgical. Early surgery without medical management is just as faulty as late surgery after there has been extensive visceral damage. Post-operative management as it applies to rest, exercise, diet, cardiac complications and iodine therapy with metabolic rate checks is a part of team management. For the present we should regard surgery as the method of choice in treating the toxic goiter case. Certain cases will respond to medical management but they are a smaller per cent of the total cases. More careful preparation and discrimination should characterize

the management of the goiter patient. Not every case with a lump in the neck should have surgical interference. A diagnosis of goiter in any of its forms does not spell surgery, necessarily.

A master surgeon has said that a successful operation only marks the beginning of the treatment of Graves' disease and here the factors to be emphasized are the same as those of preoperative management, viz. rest, mental and physical, which cannot be satisfactorily obtained in hospital wards. A prolonged vegetative period should follow recovery, whether the management be surgical or medical. It is extremely important to have surgical treatment early where surgery is indicated. The disappointing results of surgical care of toxic goiter may be due largely to two factors, one, the delay of operation and the other, faulty medical management.

Editorial

SOME SEX DIFFERENCES IN THE PATHOLOGICAL PICTURE OF SYPHILIS

It has long been recognized that there are very marked differences clinically in syphilis in the two sexes, but the full import of these variations is not usually brought to the mind of the internist as constituting definite factors in diagnosis. Both sexes are usually approached along the same line diagnostically, and as a result syphilis is often not suspected in women when it does exist. Unfortunately most of the textbooks have failed to recognize these important differences at all or only very incidentally; and only three of the most recent works on syphilology make any adequate mention of them. In the examination of any given female patient for evidences of syphilitic infection it must be borne in mind that in a very large number of syphilitic women there will be no history of primary or secondary lesions given by the patient and that a very large percentage will constantly show a negative Wassermann reaction. On the whole typical chancres are comparatively rare in women owing to the structure and conformation of the genital organs, and also because many infections of the female are seminal infections. Chancre d'emblée, or hidden or concealed chancres are very much more frequent in women than in men. Primary lesions within the genital organs are relatively rarely recognized. On such tissues as the moist mucous membranes of the vulva and cervix, and possibly also in the endometrium, the primary lesion may show such appearances that it may easily be mistaken for something else, and this mistake, particularly as to suspected malignancy, not infrequently occurs. The secondary skin eruptions are more frequently overlooked in the female than in the male. In a large proportion of female syphilitics there will be elicited no history of either primary or secondary lesion. On the other hand, constitutional symptoms, such as fever, anemia, rheumatic or neuritic manifestations and various so-called "toxic" symptoms usually replace the customary history of early syphilis. The female undoubtedly has a higher degree of natural immunity or resistance to the spirochete pallida than has man. This biological difference is greatly increased during the child-bearing period, particularly if the infection is a conceptional one. The woman who has a syphilitic embryo, fetus or child is always syphilitic herself, but she may show absolutely no clinical signs of such an infection on her part. Her Wassermann may be consistently negative for many years. The only sign of her syphilis is the fact that she produces syphilitic children, or constantly aborts. Never-

theless, at the time of the menopause she usually shows a positive Wassermann or develops unmistakable clinical signs of the disease. This immunity of the woman during the child-bearing years is one of the most remarkable features of syphilis; but unless this fact is known and understood by the clinician, he is certain to go far astray in his diagnostic evaluation of many female patients. Further, if he fails to recognize this possibility, he deprives many syphilitic children of the chance of antenatal treatment. In such women treatment is of value to the fetus and usually not to them. Moreover, he should be prepared to advise or to administer active antisyphilitic treatment to such women as have borne syphilitic children as they approach the menopause when such latent syphilis tends to become active in them. Here also in the stage of renewed activity syphilis shows very great sex differences as to organs and tissues involved. Only rather rarely does the syphilitic women develop serious syphilitic lesions in aorta or heart. While colored women and occasional white women who have been engaged for a long time in hard manual labor may show as severe aortitis or myocarditis as any male, such cases are very unusual. The average female with latent syphilis has very slight lesions in aorta and heart which give her no especial clinical manifestations and play no important role in producing cardiac insufficiency. Aortic aneurism is very uncommon in women; and cardiac death from syphilis rare also. On the other hand the liver is very frequently involved in such females with latent syphilis. As the menopause develops obscure abdominal symptoms appear; and at operation or autopsy a well-developed hepar lobatum is found. It is remarkable to what degree a gummatous hepatitis may develop with few or no symptoms. Milder degrees of this disease are usually referred by the clinician to gall bladder disease. The pancreas and adrenals are also much more frequently seriously involved in women than in men. The pancreatic condition is usually diagnosed clinically as disease of the gastro-intestinal tract; while apparently there is no well-defined clinical picture of the adrenal localization except in the most severe cases in which an addisonian syndrome is present. Gummatous strictures of the rectum are very much more frequent in women at the menopause period, than they are in the male. The condition is almost always suspected to be malignancy; and numerous cases are operated upon with such an incorrect diagnosis, as shown by microscopical examination. The latter, however, should always be made before the operation, and not after it. Gummatous lesions are also more common in women in the pectoral regions, nose and mouth than in the male. A still more striking sex-difference exists. In the male the latent syphilitic always shows testicular lesions in the form of an orchitis fibrosa; but in the female the sex gland, the ovary, seems to be immune to the spirochete. It is very doubtful if anyone has ever seen a positive syphilitic lesion of any kind in the ovary. If such lesions exist they are either

extremely rare or we are unable to recognize them. In the latter case it remains for coming pathologists to give them recognition. There are, then, very remarkable differences in the pathological pictures of syphilis in the two sexes. Some of these differences may be explained as the result of differences in environment, habits, occupation, and general hygiene; others must depend upon deep-seated biological or endocrinal differences. The especial degree of clinical freedom from the disease which the latent syphilitic woman possesses during the child-bearing disease must depend upon some especial protective mechanism active at this time. While we cannot explain these differences in reaction to a given infection, it is very necessary to know that they exist, and to take account of them whenever the question of syphilitic infection in woman comes up, and to recognize the fact that syphilis in women often cannot be diagnosed by the Wassermann reaction.

Abstracts

Effect of Ultraviolet Light on the Blood of New-Born Infants. Erythrocytes and Hemoglobin. By H. N. Sanford (Amer. Jour. of Dis. of Children, Jan., 1928, Vol. 35, p. 9).

With the increasing use of ultraviolet light as an important therapeutic measure for children, it is obviously necessary to ascertain the effect of this procedure on the young organism. In a previous paper the writer has shown that ultraviolet light is capable of increasing the blood platelets in the new-born. The present investigation deals with the effect on the erythrocytes and hemoglobin, and is based on observations on a series of 200 new-born infants during a period of eight months. The erythrocyte count and hemoglobin determinations were made within six hours after birth and at twenty-four hour intervals thereafter. These were made at the same time every day. Treatments with the ultraviolet ray were begun on alternate infants on the second day, and continued thereafter at the same time on each of the following four days. The method of Newcomer for the determination of the hemoglobin was used. Blood was taken from the skin of the heel after thorough cleansing with soap and water and alcohol. In the normal series the number of erythrocytes was found to compare favorably with that found by other investigators. The sex variations were within the limits of normal technical error, and not worth recording. The average count in the normal series ran from 4,500,000 to 5,800,000. Since the observers have reported extremely high hemoglobin values during the first week of life it is of interest that this series of cases showed an average much lower than is usually supposed, 94-115 per cent. Two patients in the series showed a well-marked anemia although the physical observations were normal. As far as the literature is concerned, anemia in the new-born is considered very rare, there being only five cases reported. Sanford believes that anemia is not uncommon but is not diagnosed because a blood count is not made. Treatments with the ultraviolet ray were given by means of an air cooled mercury vapor quartz lamp, of 110 volts, 60 cycle and 10 amperes. A voltage of 70 was always administered and maintained throughout this exposure. Dorsal and ventral surfaces were exposed for one minute each, the time being increased one minute a day until the fourth day. As a result of this investigation Sanford found that the percentage of hemoglobin in the blood of new-born infants is not so high as is usually quoted. Short exposures to ultraviolet light increase the hemoglobin content and number of red cells to a slight extent in an average number of cases, with a rapid return to normal. In cases in which the hemoglobin content and number of red cells are lower than normal the increase in both hemoglobin and number of red cells is greater, but they tend to remain nearly normal. The results would indicate a stimulation of the hematopoietic organs. The increase in hemoglobin content during irradiation might be due to the decreased volume of blood resulting from loss of water from the blood during the first days of life. As there is an increase in the number of red cells in cases in which the hemoglobin is increased, however, it does not appear that there is an actual increase of the hemoglobin content in individual cells. The subject of blood volume in the new-born is not well understood and deserves more study. The few cases examined after discharge from the hospital showed normal values. They indicate that the hemoglobin content and the red cell count drop rapidly

to a normal level after irradiation. As far as the literature is concerned Aschenheim, Gelera and Barenberg found no increase in hemoglobin and red cells after ultraviolet irradiation, while Miles and Laurens did. Graffenburger, Marti, Borisson, Orum, Aschenheim, Koster and Laurens and Sovy all found a decrease in hemoglobin content and red cells in darkness and an increase in sunlight. On the other hand, Grober and Sempell examined horses kept for from five to ten years in mines, and did not find a decrease in either the hemoglobin content or the number of red cells. Likewise, Blessing, a surgeon on the Nansen expedition, found no change in hemoglobin content or the number of red cells in the members of the expedition after their exposure to the long polar night.

Experiments with Diabetic Urine on Rabbits. By ALICE TWEED MARSTON. (Thesis in Bacteriology, Univ. of Penn., 1927.)

The cause of diabetes has attracted little attention, either clinically or experimentally. Certain experiments by D. H. Bergey at the University of Pennsylvania seemed to point to a filtrable virus as the direct causative agent. His conclusions were so revolutionary that further study and experiment along the same lines seemed desirable. Numerous investigators have thought that diabetes is possibly contagious, basing this belief on the fact that the disease often occurs in husband and wife, nurse and patient, and children in the same family. However, such coincidences may be explained on other grounds, familial susceptibility, faulty hygienic habits or pure chance. The present investigation concerned itself with the intravenous injection of diabetic urine filtered through diatomaceous earth filters, or by the introduction of unfiltered diabetic urine by stomach tube. Rabbits were used for the experiments. The negative results obtained would indicate that glycosuria cannot be produced in rabbits by intravenous injections of filtered diabetic urine. Some of the experiments as to the glucose tolerance tests showed, however, that the blood sugar in injected animals rose above normal and returned to normal more slowly than in the case of uninjected animals, thus suggesting some change in the condition of the injected rabbits. Nothing in this investigation can be taken as supporting any definite statement as to the infectious nature of diabetes mellitus.

Myxedema Heart. By GEORGE FAHR (Amer. Heart Journal, October, 1927, p. 14).

Fahr believes that if dilatation of the heart, dyspnea on exertion, anasarca of the dependent portions of the body, passive congestion of the liver, and edema of the lungs are symptoms of heart failure, then heart failure of greater or less degree is not very infrequent in myxedema. If the complete or nearly complete relief of these symptoms by medication with thyroid extract in amount sufficient to bring the basal metabolism up to normal and to cause the myxedema to disappear is evidence that both the myxedema and the heart failure have the same cause, namely, thyroid deficiency, then the term myxedema heart is justified. He reported, in 1925, two cases of heart failure of this type, apparently cured by thyroid medication. Previously Zondek had reported six cases of heart failure to thyroid deficiency which were cured by thyroid medication. Assman, Meissner, and Curschman have reported in the German literature similar cases; Lambry, Mussio-Fournier and Waker one case in the French literature; and Means, White and Krantz one case in this country. On the other hand Willius and Haines, in a study of 162 cases of high grade myxedema, found no case of "heart failure or of organic cardiovascular disease that could be justly attributed to the myxedema. There were numerous electrocardiographic abnormalities which disappeared under thyroid medication. The data presented do not justify the establishment of a cardiac syndrome characteristic of myxedema." Willius and Haines' conclusions are very hard to understand. With the largest material of myxedema cases in the world they have been unable to find a single case of car-

diac failure attribute to myxedema, whereas in other clinics where the amount of material is very much smaller numerous cases of heart failure unquestionably due to the same factors as the myxedema have been found. In the past four years Fahr has seen six such cases at the General Hospital and the University Hospital in Minneapolis. All six cases showed more or less heart failure, the symptoms and signs of which receded partially or completely on thyroid medication. These six cases are reported in this paper. Fahr concludes from this study that heart failure not very infrequently accompanies myxedema and disappears with the myxedema on treatment with thyroid extract. This heart failure is characteristic of myxedema as only thyroid extract will completely alleviate it. It therefore deserves the name of myxedema heart, the term applied by Zondek to this condition in 1918. As he was the first physician to point out the outstanding features of cardiac failure in myxedema, the name applied by him should stand despite the fact that it might be improved upon.

Innervation and Tumor Growth. A Preliminary Report. By HORST OERTEL (Canad. Med. Jour., 1928, XVIII, p. 135).

It is generally stated in the leading textbooks on pathology that neoplasms have no nerve-supply of their own, and this statement has been emphasized as one of the most important proofs of the autonomous and emancipated nature of tumor growth. What nerve structures have been demonstrated histologically in neoplasms have been regarded as remains of the original nerve-supply of the part. The older students of this question invariably reported negative results. That such developmental disturbances as nevi may contain nerve fibers has nothing to do with this question, inasmuch as they do not represent true autonomous blastomas, although such may arise in them. The question has been re-opened by the work on experimental tar-cancer. Itchikawa claims to have found nerves in tar-cancer and in a spontaneous cancer of the horse. Nakamoto, on the other hand, finds no nerves in tar-cancers. Oertel, using a modification of Bielschowsky's nerve-stain, believes that he has been able to demonstrate a nerve-supply in several types of cancers and sarcomas of man. By this method nerve fibers are stained black; other fibers and reticulum, pale brown or yellowish. The nerve fibers are also characterized, in addition to their staining by their manner of distribution, method of branching, and manner of approach to the cells. Six illustrations are given: Squamous-celled cancer of the cervix, cancer of prostate, metastatic in pelvic lymph node, primary adenocarcinoma of lung and adenocarcinoma of rectum metastatic in the kidney. There is no detailed description of the fibers shown in these illustrations, and no control proofs with other nerve stains are offered. The text of the article is argumentative rather than demonstrative. It cannot be said that the illustrations are in themselves convincing that the fibrils present are anything other than reticulum or elastic tissue fibrils. As far as any special staining differentiation is concerned between nerve and reticular fibrils there does not appear to be such in the photomicrographs. Should some of these fibrils actually be nerve fibrils it still remains to be proved that they are not the remains of the original nerve supply of the tissue. The resistance of nerve trunks and fibers to neoplastic invasion is well known; they may remain apparently unaffected when all other normal structures have disappeared before the invading tumor cells. Further, if nerve fibrils should be demonstrated in the walls of the vessels of neoplasms, it does not necessarily follow that these fibers have any relation to the parenchymatous cells of the neoplasm.

Reviews

Treatment of Disease in Infants and Children. By HANS KLEINSCHMIDT, M.D., Professor of Pediatrics, University of Hamburg. Authorized Translation of the Fifth German Edition with Additions. By Harry M. Greenwald, M.D., Attending Pediatrician to the United Israel Zion Hosp.; Consulting Physician to the Hebrew Infant Home of Brooklyn, Brooklyn, N. Y. 359 pages. P. Blakiston's Son and Company, Philedalphia, 1928. Price in cloth, $5.00.

This book had its origin in Czerny's clinic in Berlin, and was originally intended for a small group. It was, however, very favorably received in Germany, and has had five editions since 1918. It has also been translated into the Russian and Portuguese languages. In it the author has endeavored to collect only those therapeutic measures in the field of pediatrics which are strongly indicated and which really appear necessary for successful treatment. He has wished to avoid polypragmatism, however, and has, therefore, omitted a great number of therapeutic procedures and drugs the addition of which might have encouraged the latter. Kleinschmidt believes that dietic and physical methods are of first importance in the treatment of diseases of children and that medicinal treatment is only of secondary importance. In the last few decades great strides have been made in the field of dietetics, and this subject is, therefore, discussed at greater length. The dosage of each drug should depend on the individual patient; the maximum and minimum doses, according to age, are given to facilitate administration. Although volumes have been written on the symptomatology and diagnosis of the diseases of children and infants, there are very few, if any, textbooks which deal purely with treatment. Usually at the end of the description of each disease one finds only a paragraph or two on treatment, a few methods or drugs are merely mentioned, and the reader is left to himself as to which one to employ and how to proceed. This book offers the practical help of an author with a broad experience. The chapter on Nutritional Disturbances, particularly, differs from the usual book on infant feeding, in that the author describes exactly the steps the practitioner should take in the management of the disturbance in question. Generalities are omitted, and minute and specific instructions are given in each case. The translation is based on the fifth German edition with supplementary notes furnished by Professor Kleinschmidt. The translator has made a number of additions dealing with the later developments in the field of therapeutics in this country, including only these drugs and procedures which have given results in his own experience. The first six chapters deal with General Therapy, Feeding of the Normal Infant, Feeding of the Constitutionally Abnormal Infant, Nutritional Disturbances ex Alimentatione, Nutritional Disturbances not due to Alimentation, and the Care and Feeding of Asthenic Infants. There follows then a chapter on the Diseases of the Newborn, after which fifteen chapters are given to the diseases of various organs and tissues. There is a chapter on Congenital Syphilis, and the last two chapters give formulas and recipes for the normal infant and the sick infant and child. The material in this book is excellent and thoroughly up to date. It is concise, clearly stated and well-arranged. The translation is good, and the translator's notes of value. It is a valuable compendium for the practitioner, and particularly should the young physician just starting into practice find it of great service.

Asthma, Its Diagnosis and Treatment. By WILLIAM S. THOMAS, M.D., Associate Attending Physician in Immunology, St. Luke's Hospital, New York. 279 pages, 20 illustrations in black and white, 6 in color. Paul B. Hoeber, Inc., New York, 1928. Price in cloth, $7.50.

A large amount of literature dealing with the subject of Asthma has appeared in medical literature during the last five years, but as yet no book by an American author dealing exclusively with the diagnosis and treatment of this syndrome has appeared. Perhaps one reason for this is that conceptions of allergy and its manifestations are undergoing frequent changes. New data appear from time to time and give promises of improvement in methods of treatment only to be discarded afterward when their shortcomings have been demonstrated by still more recently discovered facts. Particularly does it appear that efforts toward non-specific desensitization have failed to produce the good results that were at first claimed in their favor. Authorities are at variance with each other in respect to the fundamental ideas of the nature of allergy. Nevertheless, through the maze of conflicting theories there shines an encouraging light. Improved results from the treatment of asthma have been made possible by means of the diagnostic aid of specific skin reactions to proteins and to vaccines. The intelligent interpretation of these dermal phenomena has made it possible for asthma patients to obtain material and permanent relief, whereas a few years ago the best that could be hoped for was temporary palliation of their sufferings. The author designed his book to be a practical guide to the management of asthma patients, and he has stated the theories regarding allergy in order to elucidate present-day methods of treatment. Confusion in terminology characterizes the current literature concerning the nature of asthma, and he has endeavored by using simple language to lessen this confusion. His first chapter is concerned with the definition and use of the term "asthma", a condition no longer looked upon as a disease but as a syndrome or symptom complex, related in a manner that is only partially understood to anaphylaxis, hypersensitiveness and immunological processes. For the sake of accuracy, the term should be applied to one condition only, namely, that associated with bronchospasm, the modifying adjective "bronchial" being superfluous should be dropped. Dyspnea due to cardiac insufficiency is not asthma, nor is the designation applicable to difficulty of breathing caused by secretions in the bronchial passages or by the pressure of tumors upon them. Asthma, then, is a syndrome occurring in constitutionally predisposed people, and having as its exciting cause exposure to or contact with some substance or physical condition to which they are abnormally sensitive. It is characterized by little understood cellular and humoral changes and exaggerated respiratory reactions. Chapters II and III are concerned with the nature and causes of asthma and the pathology of this condition respectively. The methods of approach to the treatment of a case of asthma, case-history taking, physical examination, etc., are discussed in the following chapters. Protein skin tests, their technique, protein skin reactions and their interpretation, details of testing and treatment, airborne proteins, food proteins, desensitization, autogenous vaccines and skin tests, pollen asthma, its diagnosis and treatment, the complications of asthma, the non-specific radical methods of treatment, and causes of failure of treatment constitute the subject matter of the remaining chapters. A very full bibliography, complete up to November, 1927, follows. The book is well printed and illustrated. It offers an up-to-date discussion of the important subject of asthma, and its perusal will be of service to every practitioner of medicine who comes into contact with this syndrome.

Early Medicine in Maryland. By THOMAS S. CULLEN. Address of the President of the Medical and Chirurgical Faculty of Maryland, 1927. 15 pages.

This is a reprint of the President's Address at the Annual Meeting of the Medical

and Chirurgical Faculty of Maryland, the State Medical Society, which was granted its charter in 1799. The address sketches the history of the medical profession in Maryland, from the visit of "Walter Russell, Gentleman, Doctor of Physicke" who accompanied John Smith in 1608, up to 1927. Among the items of special interest is that in 1637 there was held an inquest on a man killed by a tree, probably the earliest recorded autopsy in America. The chief sources of authority for the history of medical science and practice in Maryland are the "Medical Annals of Baltimore from 1608 to 1880" by Thomas Quinan, which was published in 1884, and Cordell's "Medical Annals of Maryland" published in 1903. From these two works much of historical interest concerning the achievements of Baltimore physicians may be gathered; and the list given on page 3 of the "first" medical and surgical deeds accomplished by them is a long and notable one. The accounts of the early epidemics of yellow fever in Cordell's work are most interesting. The Medical and Chirurgical Faculty of Maryland is, at least, accomplishing one great deed of usefulness in perpetuating the records of the medical history of Maryland and Baltimore. In this respect it sets an example to other State Societies.

Aluminum Compounds in Foods. Including a Digest of the Report of the Referee Board of Scientific Experts on the Influence of Aluminum Compounds on the Nutrition and Health of Man. By E. E. Smith, Ph.D., M.D., Fellow and Former President, New York Academy of Sciences; Fellow of the New York Academy of Medicine, etc. 378 pages. Paul B. Hoeber, Inc., New York, 1927. Price in cloth, $7.00 net.

The recent litigations, not yet ended, concerning the use of alum in baking powders and the alleged harmfulness of such, gave rise to many experimental researches regarding the toxicity of aluminum. These studies are widely scattered in the literature. The author believes that the subject has become of such general interest as to demand its presentation within the pages of a single volume. It will be of value not only to those interested in the particular subject, but as well to a much larger number interested in scientific methods of investigating the composition and value of food. The volume contains researches by the author which have not appeared elsewhere, and gives details of unpublished work by other investigators, including a comprehensive résumé of the investigations by the Referee Board of the United States Government. It is stated to be a complete, authoritative and impartial survey of this disputed question, and as such is valuable to physicians, chemists and all others interested in this subject. A valuable bibliography is included.

College News Notes

TWELFTH ANNUAL CLINICAL SESSION, NEW ORLEANS, MARCH 5-9, 1928

The Twelfth Annual Session has passed into the history of the College. There can be no doubt, judging by the almost universal comment, that as far as the General Sessions were concerned this was the most successful meeting the College has yet carried out. Many of the addresses were concerned with clinical and experimental material of the highest order, even epoch-making in certain instances. The others represented important reviews and résumés of clinical questions of prime importance, and from every one of them some important fact or viewpoint could be obtained. An unusual degree of interest was shown by the large attendance at each session; even the last one had a well-filled auditorium. There were nearly one thousand registrations. The official meetings were well attended, and much business of great importance to the College was carried out, marking important advances in policy. A very large list of new Fellows and Associates passed a more critical survey of their qualifications than ever before, and the College may congratulate itself upon the high quality of the newly-elected, including some of the leading internists of the country. The names of these will appear in the April number, together with those of the new officers and committees. The publication of the addresses and papers will begin in the April number of the Annals; and it is hoped that this meeting will be recorded in full in the journal. New Orleans more than made good as a most interesting city. The historical interest of the old French quarter added much to the pleasure and charm of this—the first Southern meeting of the College.

OBITUARIES

Dr. Richard Bew, Atlantic City, New Jersey—September 4, 1927. Killed by propeller of a yacht while swimming. Elected a Fellow of The College December, 1926.

Dr. Bew, who was born in Germantown, Pa., in 1882, is survived by his wife, who was Elsie Gould, daughter of Mrs. T. K. Roberts, of Atlantic City, and two sons, Richard, Jr., 21, a life guard here and in his third year at Lafayette College, and Walter, six years old. He came to Atlantic City in 1922 to practice. He saw medical service during the World War. He was a Republican in politics and an Episcopalian.

Dr. Charles Giffen Beall, Fort Wayne, Ind. (Fellow, November 3, 1922). Died February 7, of Pneumonia following a cerebral hemorrhage; aged 46.

Dr. Beall received his medical degree from the Fort Wayne College of Medicine in 1904 and afterwards did postgraduate work at Allgemeines Krankenhaus, Munich. During the World War, he served as Captain of the Medical Corps, United States Army. Since 1923, Dr. Beall has been Chief of the Medical Service at Fort Wayne Lutheran Hospital, and at the time of his death was on the staffs of the Indiana School for Feeble-minded Youth, and the Irene Byron Sanatorium of Tuberculosis.

He was a member of the Association for the Study of Internal Secretions, the American Society for the Control of Cancer, the American Medical Association, the Indiana State Medical Society, Fort Wayne Medical Society and a member of the Board of Governors of The American College of Physicians.

Dr. Ben Carlos Frazier, Louisville, Ky. (Associate, April 15, 1920). Died February

10 from an Intestinal Obstruction following Prostatic Operation; aged 63.

Dr. Frazier received his medical degree from the University of Louisville School of Medicine in 1894. He established certified milk in Louisville and other communities as officer in National Medical Milk Commission.

He was on the staff of the Childrens' Free Hospital, the University of Louisville Medical School and City Hospital, Hazelwood County Hospital for Tuberculosis, the Christian Widows and Orphans Home and the Kentucky Institution for the Blind.

He was a member of the American Medical Association, the Jefferson County Medical Society, the Medico-Chirurgical Society of Louisville, the Obstetrical Society of Louisville, the Jefferson County Milk Commission and an Associate of The American College of Physicians.

BUDAPEST CONGRESS PROGRESS REPORT

FEBRUARY 25, 1928.

The Vth International Medical Congress for Industrial Accidents and Occupational Diseases is definitely announced to be held in Budapest, Hungary, Sept. 2-8, 1928. National committees have been formed in the principal countries.

Since the first American announcement of Dec. 1st, 1927, Dr. Fred H. Albee, New York City, and Dr. Emery R. Hayhurst, Ohio State University, Columbus, both members of the Permanent International Committee, have been appointed Joint Chairmen of the National Committee for the United States, and have appointed Dr. Richard Kovacs, New York City, as Secretary, and the others named in the letter-head to serve as members.

The Travel Study Club of American Physicians, of which Dr. Albee is President and Dr. Kovacs, Secretary, has rearranged its summer trip for 1928 especially to focus upon the Budapest Congress. Those who have already indicated their intention of attending the Congress and others are invited to join the Travel Study Club either for the entire trip or at any point. The itinerary thus far arranged calls for sailing from New York on the S. S. "München" of the North German Lloyd, on Aug. 16th: three days in Berlin, two days in Carlsbad, five days in Budapest, two days in Vienna, two days in Bad Reichenhall and Salzburg, and two days in Munich; then via Milan to Nice for two days and from Sept. 17th to 27th in Spain; sailing from Gibralter on Sept. 28th on the S. S. "Conte Grande" of the Italian Mediterranean Service, due back in New York on October 5th. (See descriptive circular enclosed).

Correspondence regarding the trip should be had with Dr. Richard Kovacs, 223 E. 68th St., New York City.

The Annual Meeting of the Association of American Physicians will be held at the Mayflower Hotel, Washington, D. C., May 1, 2 and 3.

The American Congress on Internal Medicine and Surgery will be held in Washington, D. C., May 1 and 2. Headquarters will be at the Mayflower Hotel.

The American Association for the Study of Cancer will be held in Washington, D. C., April 30, at the Hotel Raleigh.